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Review Article

Functional organ preservation in laryngeal and hypopharyngeal cancer

Abstract

The principles of open versus laser microsurgical approaches for partial resections of the larynx are described, oncologic as well as functional results discussed and corresponding outcomes following primary radiotherapy are opposed. Over the last decade, the endoscopic partial resection of the larynx has developed to an accepted approach in the treatment of early glottic and supraglottic carcinomas thus leading to a remarkable decline in the use of open surgery. Comparing the various surgical approaches of laryngeal partial resections, the oncological outcome of the patients, as far as survival and organ preservation are concerned, are comparable, whereas functional results of the endoscopic procedures are superior with less morbidity. The surgical procedures put together, are all superior to radiotherapy concerning organ preservation. Transoral laser microsurgery has been used successfully for vocal cord carcinomas with impaired mobility or fixation of the vocal cord, supraglottic carcinomas with infiltration of the pre- and/or paraglottic space as well as for selected hypopharyngeal carcinomas. It has been well documented that laser microsurgery achieves good oncological as well as functional results with reasonable morbidity. However, patients with those tumours have been successfully treated by open partial resections of the larynx at medical centres with appropriate expertise. The initially enthusiastic assessment of study results concerning the efficacy of various protocols of chemoradiation with the intent of organ preservation for laryngeal and hypopharyngeal carcinomas are judged more cautious, today, due to recent reports of rather high rates of late toxicity complications.

Keywords: laryngeal cancer, hypopharyngeal cancer, treatment, organ preservation, partial laryngectomy, transoral laser microsurgery, chemoradiation

Petra Ambrosch[1]
Asita Fazel[1]

1 Department of Otorhinolaryngology – Head and Neck Surgery, Christian-Albrechts-University of Kiel, Kiel, Germany

1. Introduction

During the last 10 years the treatment options for laryngeal and hypopharyngeal cancer have changed significantly. The development of transoral laser microsurgery, improvements in delivery of radiation therapy and the advent of new radiation protocols with or without chemotherapy have supplemented the previous standard techniques of open partial laryngectomy, total laryngectomy, and radiotherapy. Although no definitive conclusions have been reached with regard to the role of these new treatment modalities, the importance of organ preservation and quality of life issues have become a major factor in decision-making and therapy planning.
With open partial laryngectomy, transoral laser microsurgery and radiation therapy with or without chemotherapy are methods available which stand for preservation of the larynx. This review focuses on the treatment of previously untreated tumors. The description of surgical procedures intends to describe anatomical structures and the basic surgical principles. This review neither intends to replace a surgical textbook nor does it provide comprehensive surgical instructions. Experimental therapies such as photodynamic therapy, the use of photoangiolytic lasers, robot-assisted surgery, and the use of chemotherapy as a single modality treatment are not discussed in this review.
The authors of this article review and discuss the relevant studies of the last decade with respect to oncologic treatment outcomes, morbidity, larynx preservation, and organ function.

2. Early Glottic Carcinomas

2.1 Definition

Approximately 3400 laryngeal cancers are newly diagnosed in Germany each year. Sixty per cent are glottic carcinomas of which 50% are detected as early stage tumors. Therefore, treatment of early glottic carcinomas is still of highly important and relevant. Treatment goals

are to achieve local tumor control and preservation of the larynx with best possible function.
There is no generally accepted definition for the term "early" glottic cancer. While some authors believe that this definition includes premalignant changes (severe dysplasia), others classify T1 tumors as early glottic carcinomas, and some even include T2 lesions in this category. In accordance with the current literature we define early glottic cancer as carcinoma in situ (Tis), non-metastasizing tumors involving one (T1a) or both (T1b) vocal cords as well as unilateral or bilateral glottic carcinomas with infiltration of the supra- and/or subglottis with preservation of vocal cord mobility (T2a).

2.2 Special Diagnostic Aspects

Laryngoscopy with adequate documentation is still the most valuable diagnostic tool. Irrespective of later treatment, a tissue diagnosis has to be performed to verify a vocal cord proliferation's malignancy. Routine CT scans of early glottic carcinomas are generally not indicated; in carcinomas of the anterior commissure they may be considered helpful. CT scans should always be performed in patients with recurrent tumors.
Histopathologic examination of a biopsy specimen by microlaryngoscopy is still the diagnostic gold standard. It is well known, that a significant number of biopsies in early glottic cancer patients result in complete tumor excision. Stutsman and McGavran [1] observed as early as in 1971 that after preceding biopsy from the vocal cord no residual carcinoma could be found in 13 out of 60 hemilaryngectomy specimens.
Steiner's group reported that in 126 (49%) of 253 patients with T1a glottic carcinoma a diagnostic microlaryngoscopy with biopsy was performed prior to admittance elsewhere. In 39 (31%) patients no residual carcinoma was found in the laser resection specimen although clinical examination showed tissue proliferations suspicious for malignancy. Similar results were reported by Nassif et al. [2] who found 33% (5 out of 15) resection specimens to be free of tumor after previous biopsy. These results show that a significant number of patients are inevitably overtreated when radiotherapy is the standard treatment protocol. This poses an unjustifiable risk of overtreatment to early glottic cancer patients.

2.3 Open Partial Laryngectomy

There are various surgical procedures for the treatment of early glottic cancer, including open cordectomy via medial thyrofissure, open vertical partial laryngectomy, hemilaryngectomy (in selected cases) and transoral laser microsurgery.
With *cordectomy via thyrofissure and open vertical (frontolateral) partial laryngectomy* a horizontal midline skin incision along the tension lines is performed. After dissection of the strap muscles the thyroid cartilage is exposed and split vertically in the midline or paramedian down to the inner perichondrium. Following the incision of the cricothyroid membrane and inspection of the tumor, the soft tissues of the larynx are incised and the vocal fold is removed adapted to the extent of the lesion. If the tumor infiltrates the anterior commissure, a small part of the contralateral vocal fold is removed additionally. With open vertical partial laryngectomy the entire vocal fold together with a part of the thyroid cartilage is resected. The size of the cartilage window is defined by tumor extent. In carcinomas of the anterior commissure, a bilateral paramedian incision of the thyroid cartilage is performed and the cartilage resected together with the anterior part of both vocal cords. Pedicled flaps from the ventricular fold can be used to reconstruct the defect. In comparison to transoral laser microsurgery the morbidity of open vertical partial laryngectomy is higher due to the need of temporary tracheostomy and a higher rate of postoperative wound infections.
Supracricoid partial laryngectomy with cricohyoidoepiglottopexie (SCPL-CHEP) involves the resection of both vocal folds, both ventricular folds, the paraglottic tissues bilaterally, the entire thyroid cartilage, the petiole of the epiglottis, and the lower portion of the preepiglottic fat. For reconstruction, the cricoid cartilage is first attached to the epiglottic remnant and then to the hyoid bone. This operation always requires temporary tracheostomy and nasogastric tube feeding.
With *transoral laser microsurgery* the vocal folds are exposed with a laryngoscope in the intubated patient. Small midcordal tumors can be resected en bloc. More extensive vocal cord lesions are removed piecemeal with a clear margin of approximately 1–3 mm [3]. We try to maintain narrow margins and preserve as much healthy tissue as possible to improve the prospects for postoperative voice rehabilitation. Postoperative voice function is mainly influenced by the amount of tissue resected. Figure 1 shows the histological structure of the vocal fold and its neighboring tissues. Morbidity associated with transoral laser microsurgery of early glottic cancer is low. A tracheostomy is never required and complications are rare, enabling the surgery to be performed on an outpatient basis [4].
The resection of larger glottic carcinomas with impaired vocal cord mobility by laser microsurgery requires subdividing the tumor into several parts. Tumors that have invaded the paraglottic space are subdivided by incisions extending laterally to the thyroid cartilage and inferiorly to the cricoid cartilage (Figure 2). The resection can be extended to the perichondrium of thyroid and cricoid cartilage, to thyroid and cricoid cartilages themselves, to the arytenoid cartilage, the cricothyroid membrane and the extralaryngeal soft tissues. A tracheostomy is seldom necessary and postoperative complications are rare.

2.3.1 Special Aspects of Histopathologic Examination of Surgical Specimens

The tissue effects of surgical carbon dioxide lasers used today have been substantially improved by more precise focusing techniques. The zone of charring and edema measures only 25 µm and does not affect the assess-

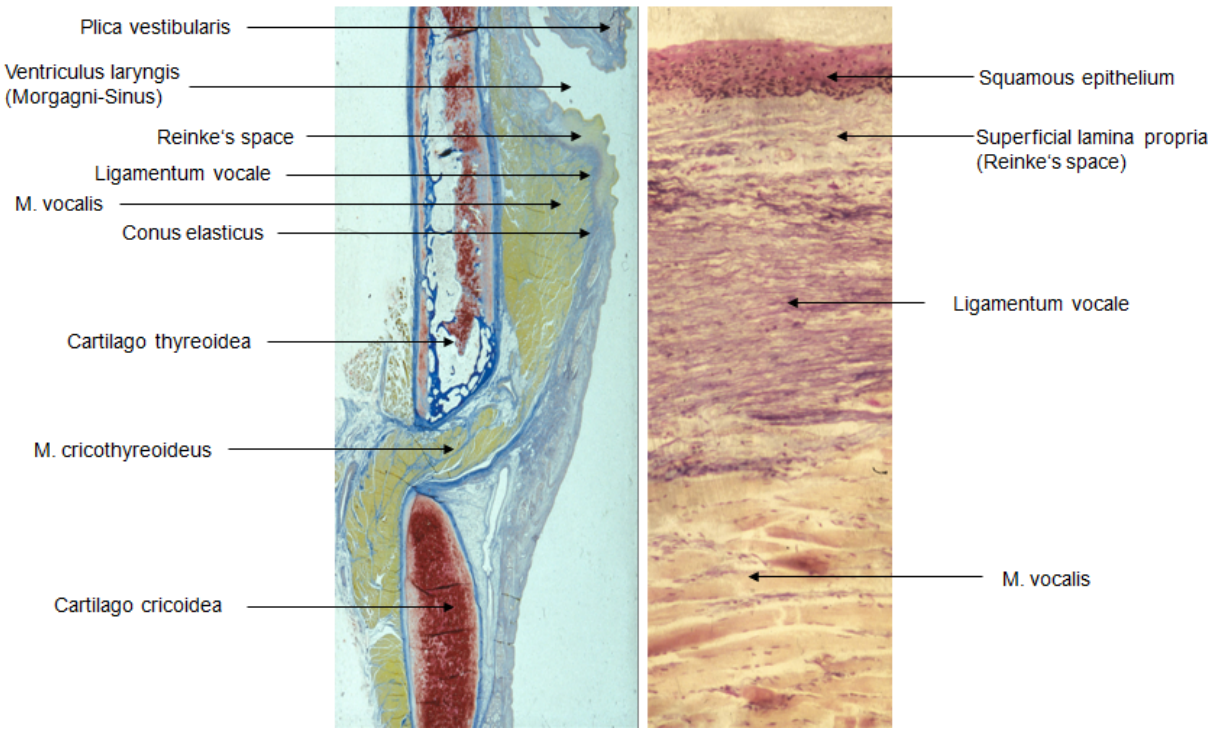

Figure 1: Left: Histologic coronal section of an adult larynx. Specimen: P. Steven. Photograph: B. Tillmann. Stain: Orcein-Pikroindigokarmin. From B. Tillmann, 2010 [262]. Right: Histologic coronal section through the vocal fold of an adult. Specimen: B. Tillmann. Stain: Elastica. From B. Tillmann, 2010 [262].

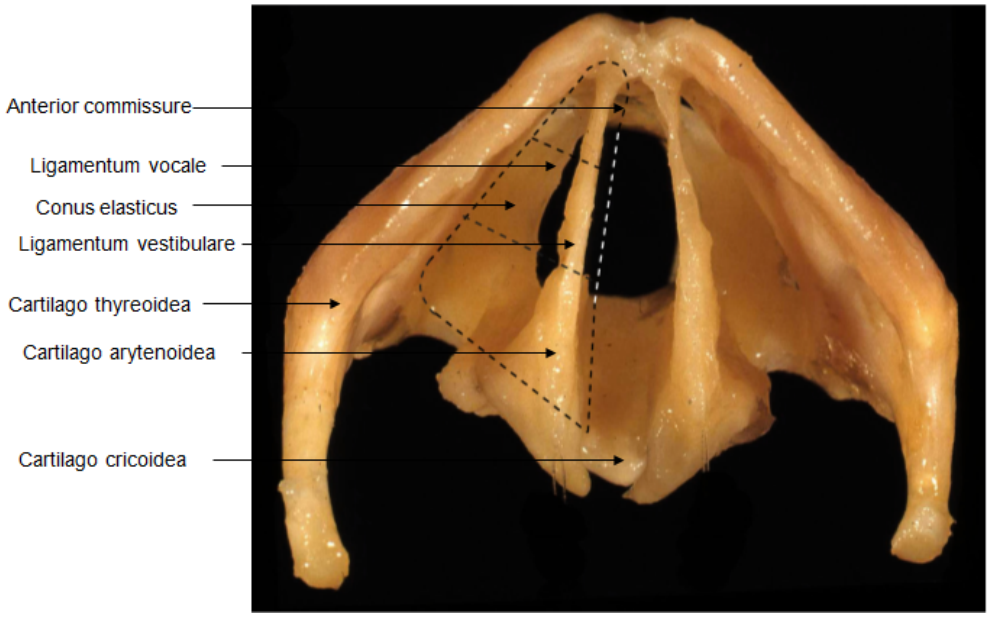

Figure 2: Bony and fibroelastic structures of the larynx. Axial view. Specimen of the scientific collection of the Inst. of Anatomy of CAU Kiel, Photograph: B. Tillmann. From B. Tillmann, 1997 [263]. The dotted lines show the resection in a case of advanced vocal cord carcinoma with resection of the vocal fold, the false cord and the arytenoid cartilage.

ability of even small specimens [5]. Artifacts and necrosis due to tissue squeezing or coagulation diathermy seem to have a bigger impact on the assessability.

Today narrow safety margins are widely accepted in laryngeal surgery [3], [6]. If a surgical margin is found to be positive for tumor cells by histopathology, the re-excision of further tissue is indicated to remove or rule out any residual tumor. This approach seems to be the safest method even though more tissue is lost and in principle a tumor recurrence can be treated successfully by a later endoscopic excision, assumed, that the recurrence is detected early [7].

Since re-excision specimens often are tumor free [7] and the glottis is easily inspected by laryngoscopy, it is discussed whether frequent follow up exams are sufficient in these cases. Preuss et al. [8] reported on positive resection margins in 84 (46%) of 181 patients after en bloc resection of T1 and T2 glottic carcinomas. In 55 patients

a re-excision was performed immediately. Only 22 (40%) of the re-resection specimens were positive. Other authors have seen similar results in smaller studies [9], [10], [11], [12]. In our view a "wait and watch" policy should only be chosen, if the patient was fully informed about the pros and cons.

2.3.2 Classification of Endolaryngeal Cordectomy

During the last couple of years various classification systems of endolaryngeal laser resections were proposed [13], [14]. In 2000 Remacle et al. [15] published a classification proposal on behalf of the European Laryngological Society, which is now widely accepted. Eight different types of endoscopic cordectomies are divided according to the extent of the resection. These classifications are useful with regard to comparability of treatment outcomes.

2.4 Oncologic Results

2.4.1 Preliminary Remarks

The best suited treatment modality for early glottic cancer is still under debate. A series of retrospective and prospective non-controlled studies have shown that both primary surgery and radiotherapy are effective methods in treating glottic carcinomas. Recently, two randomized studies have been initialized to compare transoral laser microsurgery and primary radiotherapy with regard to oncologic results, morbidity, voice quality, complications and cost [16], [17]. The implementation of the prospective randomized EaStER study (Early Stage glottic cancer: Endoscopic excision versus Radiotherapy; Chief Investigator Prof. M. Birchall) was recommended in the UK in 2004 by the CRUK (Cancer Research UK) under the precondition of a successful preliminary feasibility study. Due to failure in recruiting enough patients for randomization (most patients or physicians preferred one of the two treatment modalities) the study had to be stopped in 2009. Another randomized study, conducted by Prof. W. Coman in Brisbane, Australia, could not be completed due to similar reasons [17].
Essential for evaluating the efficacy of a treatment modality for early glottic cancer are the following parameters: Local control and larynx preservation, complications und undesirable side effects of treatment, treatment options for recurrences, functional results, and the cost. Survival rates do not play a major role for the evaluation of the efficacy, because the risk of death due to a second primary lung cancer is considerably higher than due to early glottic cancer.

2.4.2 Results of Open Vertical Partial Laryngectomy

During the 70ies and 80ies early glottic carcinomas were surgically treated by open vertical partial laryngectomy (cordectomy via laryngofissure, frontolateral partial laryngectomy, and in selected cases hemilaryngectomy). In the past two decades there is a declining use of vertical partial laryngectomy. This is reflected by a decreasing number of reports published in the current English literature.
In 1994, Thomas et al. [18] reported a series of 159 patients with T1 glottic cancer who underwent vertical partial laryngectomy at the Mayo Clinic between 1976 and 1986. The 5-year local control rate was 93% and in 94% of the patients, the larynx could be preserved. Spector et al. [19] treated 404 patients with T1 glottic cancer with a 5-year local control rate of 92% and larynx preservation rate of 93%. In 71 patients with T2 glottic carcinoma the 5-year disease-specific survival rate was 92%. The larynx preservation rate was 92% [20]. Brumund et al. [21] describe the treatment results of vertical partial laryngectomy in 232 patients with T1 and 35 patients with T2 vocal cord carcinomas. The 5-year local control rate was 91% and 68.7%, respectively. In 92.9% and 93.3% the larynx was preserved. Overall 18.1% of patients, however, suffered from postoperative complications such as wound infection (7%) or subcutaneous emphysema.
Crampette et al. [22] report on 81 patients with early glottic carcinomas treated with a modified subtotal laryngectomy with cricohyoidoepiglottopexy. No local recurrences where observed in T1 cancer patients whereas the 5-year local control rate in T2 cancer patients was 92%. Although the postoperative clinical course was uneventful, all patients showed remarkable voice impairment. Makeieff et al. [23] assessed the voice related quality of life using the Voice Handicap Index [24] in 64 patients with T1b or T2 glottic carcinoma who underwent supracricoid partial laryngectomy. Fifty-five per cent of working patients were unable to practice their profession or had to change their job due to voice impairment.
It can be concluded that open vertical partial laryngectomy in early glottic tumors demonstrates very favorable oncologic results. In patients with T1 glottic cancer the local control rate averages between 92%–100% with a laryngeal preservation rate between 94%–100%. In patients with T2 glottic cancer with unimpaired vocal cord mobility local control rates average between 69%–93% and organ preservation rates between 92%–93%.

2.4.3 Results of Transoral Laser Microsurgery

In 1993, Steiner [25] reported a first series of 240 patients who underwent transoral laser microsurgery for carcinomas of the larynx between the years 1979 and 1991. Among the 240 patients were 159 with early glottic carcinomas (Tis 29, T1 96, T2a 34). Only 6% developed a local recurrence with only one patient requiring a total laryngectomy. Since Steiner's pioneering work transoral laser microsurgery has become a widely accepted and successfully used method in treating early laryngeal cancer. In recent years it has become a standard method for the treatment of early vocal cord cancer [26], [27]. Steiner's group from Göttingen/Germany published a

Table 1: Results of transoral laser microsurgery for T1 vocal cord carcinoma

Author	Number of patients	T category	Local control	Larynx preservation
Mahieu et al. 2000 [264]	127	T1a	92%	99%
Eckel et al. 2001 [265]	161	T1	87%	94%
Ambrosch et al. 2001 [28]	248 35	pT1a pT1b	92% 80%	99% 94%
Gallo et al. 2002 [266]	117 22	T1a T1b	94% 91%	– –
Pradhan et al. 2003 [267]	52 17	T1a T1b	90% 65%	94% 88%
Motta et al. 2005 [268]	432	T1	85%	97%
Sigston et al. 2006 [9]	52	Tis, T1	94&	100%
Ledda et al. 2006 [269]	82	T1	96%	100%
Hartl et al. 2007 [11]	142	Tis, T1a T1b	89%	97%
Grant et al. 2007 [270]	45	T1	90%	95%
Manola et al. 2008 [6]	31	T1	95%	–
Sjögren et al. 2008 [61]	189	T1a	89%	96%
Peretti et al. 2010 [84]	404	pT1	95%	98%

Table 2: Results of transoral laser microsurgery for T2 vocal cord carcinoma

Author	Number of patients	T category	Local control	Larynx preservation
Eckel et al. 2000 [271]	93	T2	82%	93%
Ambrosch et al. 2001 [28]	128	pT2a	84%	96%
Peretti et al. 2005 [272]	55	T2a	84%	93%
Motta et al. 2005 [268]	236	T2	66%	83%
Grant et al. 2007 [270]	21	T2	93%	95%
Peretti et al. 2010 [84]	109	pT2	86%	95%

series of papers in the following years focusing on the oncologic results in early glottic cancer. The Kaplan-Meier 5-year local control rate for pT1a carcinomas (n=248) was 92%, for pT1b carcinomas (n=35) 80% and for pT2a carcinomas (n=109) 84%. Secondary laryngectomy was performed in 1.2% of patients with pT1a, in 5.7% with pT1b, and in 3.7% with pT2a carcinomas. The Kaplan-Meier 5-year ultimate local control rate was 99% for pT1a, 97% for pT1b, and 98% for pT2a carcinomas [28].

Many authors have published recently on transoral laser microsurgery in patients with Tis-T2a glottic cancer demonstrating good oncologic and functional results. An overview of the literature of the last 10 years is shown in Table 1 and Table 2. Karatzanis et al. [29] compared transoral laser microsurgery and open partial laryngectomy in two cohorts of patients with T1a and T1b glottic cancer treated at the University of Erlangen/Germany. Local control rate and disease specific survival rate showed no significant difference between the two cohorts. In conclusion it can be stated that with transoral laser microsurgery the 5-year local control rate for T1 glottic cancer is 85%–96% with a larynx preservation rate of 94%–99% (Table 1). For T2 glottic carcinomas the 5-year local control rate is 66%–84% and the 5-year larynx preservation rate 83%–96% (Table 2). The tumor-related death rates are <1% for T1 and <3% for T2 carcinomas.

2.5 Early Glottic Carcinomas with Involvement of the Anterior Commissure

In early glottic carcinomas with involvement of the anterior commissure the special anatomy of this region is of clinical importance. The absence of perichondrium at the vocal ligament insertion, the extension of the vocal ligament fibers into the thyroid cartilage, and the connections between the intra- and extralaryngeal blood vessels and lymphatics [30], [31], [32] (Figure 3, Figure 4) were often referred to as possible reasons for recurrences in the anterior commissure. Kirchner and Carter [33] observed in serial organ sections that T1a and T1b carcinomas rarely infiltrate the thyroid cartilage. On the other hand, carcinomas of the anterior commissure that have invaded the cartilage typically show supraglottic extension to the

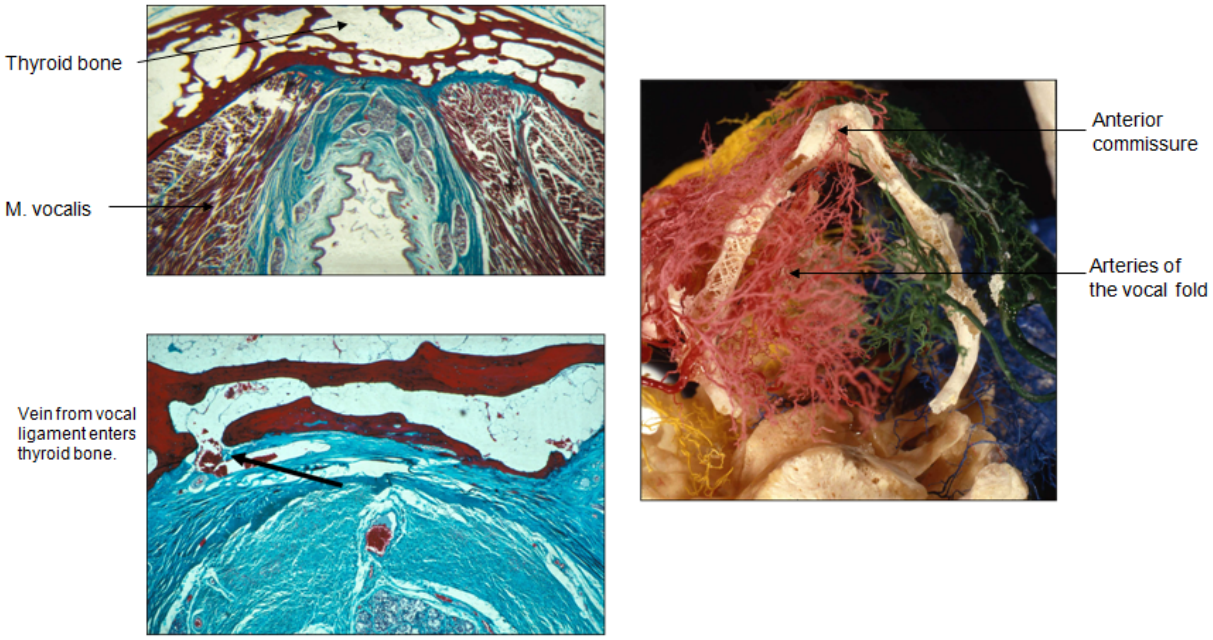

Figure 3: Left superior: Histologic horizontal section through an adult larynx. Stain: Goldner. Specimen: B. Tillmann. Left inferior: Histologic horizontal section through an adult larynx at the plane of the anterior commissure. Stain: Goldner. Specimen: B. Tillmann. Right: Laryngeal skeleton with blood vessels. Corrosion specimen of the scientific collection of the Inst. of Anatomy of CAU Kiel, Klaws fecit. Photograph: B. Tillmann.

petiole area, subglottic extension, or both (T2 carcinomas) [33], [34]. In a recent study by Hartl et al. [35] these findings could be confirmed. The histopathologic examination of 358 resection specimens from the larynx showed in only 8.9% cancer infiltration of the thyroid cartilage. The study revealed, that the infiltration rate of the thyroid cartilage was the same for both glottic carcinomas with and without involvement of the anterior commissure. Infiltration of the thyroid cartilage correlated with T category and vocal cord mobility.

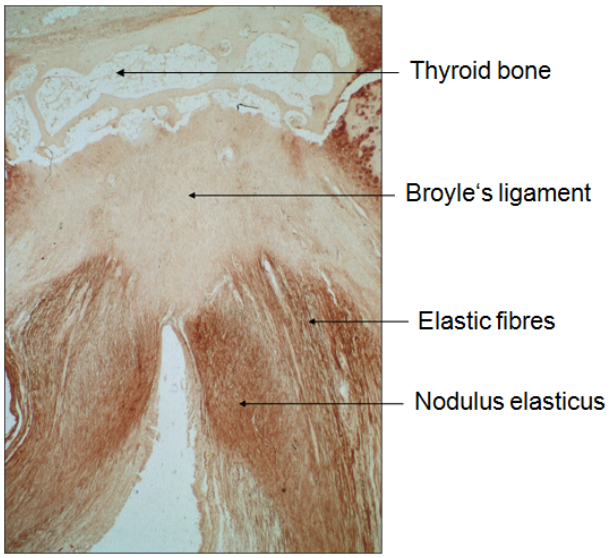

Figure 4: Histologic horizontal section through an adult larynx at the insertion of the vocal ligaments at the anterior commissure. Stain: Gomori. Specimen: F. Paulsen and B. Tillmann. From Paulsen F, Tillmann B, 1996 [30].

2.5.1 Results with Involvement of the Anterior Commissure

Involvement of the anterior commissure means always a challenge for any surgical treatment [36] whereas most authors agree that it does not affect the results of primary radiotherapy [37], [38], [39], [40]. Laccourreye et al. [41] reported on 416 patients with T1 and T2 glottic carcinoma who underwent open vertical partial laryngectomy. The local recurrence rate in carcinomas with involvement of the anterior commissure was 23%. As an alternative to frontolateral partial resection supracricoid laryngectomy was performed in some centers with the intent to improve the local control rate in anterior commissure carcinomas. Laccourreye et al. [42] reported on 62 cases of SCPL-CHEP in T1 and T2 glottic carcinomas with anterior commissure involvement. Eighty-one per cent of the patients had undergone neoadjuvant chemotherapy prior to surgery. An excellent 5-year local control rate of 98% could be achieved. No total laryngectomy or permanent tracheotomy had to be carried out for functional reasons. One must take into consideration however, that SCPL-CHEP with prior chemotherapy is associated with considerable morbidity and can be applied not to every patient. Even though all patients could be decannulated in Laccourreye's series, 17 patients needed postoperative swallowing training, 4 received a temporary and one a permanent PEG feeding tube. Patients after SCPL-CHEP develop compensatory supraglottic phonation mechanisms resulting in moderate to severe dysphonia [43], [44], [45].

Steiner et al. [46] analyzed the influence of anterior commissure involvement on local recurrences, laryngeal

Table 3: Results of radiotherapy for T1 vocal cord carcinoma

Author	Number of patients	Local control	Larynx preservation	TNM related deaths
Skladowski et al. 1999 [273]	235	84%	–	–
Dinshaw et al. 2000 [274]	460	82%	–	–
Brouha et al. 2000 [275]	362	83%	–	–
Mendenhall et al. 2001 [37]	291	93%	95%	2%
Johansen et al. 2002 [276]	482	85%	89%	–
Jorgensen et al. 2002 [102]	312	88%	96%	–
Gowda et al. 2003 [38]	200	93%	96%	4%
Cho et al. 2004 [277]	178	83%	–	–
Cellai et al. 2005 [53]	831	84%	92%	6%
Yamazaki et al. 2006 [39]	180	86%	96%	1%
Groome et al. 2006 [278]	491	82%	–	–
Tamura et al. 2007 [279]	56	93%	98%	2%
Sjögren et al. 2009 [40]	316	86%	89%	4%
Smee et al. 2010 [280]	356	83%	–	5%
Chera et al. 2010 [281]	T1a: 253 T1b: 72	94% 93%	95% 94%	– –

preservation, and survival in 263 patients with early glottic cancer who underwent transoral laser microsurgery. It was shown that involvement of the anterior commissure affected the local control and organ preservation rates but not the survival rates. The Kaplan-Meier 5-year local control rate of carcinomas with or without involvement of the anterior commissure was 86% vs. 95% for T1a carcinomas, 75% vs. 93% for T1b carcinomas and 78% vs. 83% for T2a carcinomas. Larynx preservation was possible in 93% vs. 99% of T1a cancer patients, in 88% vs. 94% in T1b cancer patients and 93% vs. 97% in T2a cancer patients. These results could be confirmed in a subsequent study encompassing 444 patients [47]. Similar results were found by Sachse et al. [48] in a retrospective study. Those authors reported poorer local control rates in T1 and T2 glottic carcinomas with involvement of the anterior commissure than in carcinomas without. No differences were found, however, comparing open vertical partial laryngectomy and transoral laser microsurgery. In contrast, Chone et al. [49] and Peretti et al. [50] did not find significantly different local control rates in laser microsurgically treated early glottic cancers with or without anterior commissure involvement.

Herranz et al. [51] in a literature review have analyzed and summarized the treatment results in early glottic cancer with involvement of the anterior commissure. They conclude that the three treatment options (surgery open or endoscopic, radiotherapy) have similar outcomes. The choice of treatment should be based on the experience and skill of the treating physician. With transoral laser microsurgery it is of importance to gain good exposure of the tumor and to keep sufficient surgical radicality in order to prevent local recurrence. In difficult cases a follow-up microlaryngoscopy after 6–8 weeks in the sense of a "second look" operation can be useful to rule out any residual tumor [3], [7].

2.6 Results of Radiotherapy

Within the last 50 years primary radiotherapy was used to treat early glottic cancer patients as an alternative to surgery. Due to good local control rates, disease-specific survival rates, good long-term function of the upper aerodigestive tract (voice and swallowing function), and the non-invasive nature of the method, primary radiotherapy was considered to be the gold standard in Northern America, Scandinavia and the UK. Therapy can be carried out on an outpatient basis and lasts for 4–6 weeks.

Table 3 and Table 4 show an overview of the literature of the last decade. Regarding the oncologic results it can be summarized, that 5-year local control rates between 82% and 93% in T1 carcinomas and laryngeal preservation rates of 89%–96% have been achieved (Table 3). In T2 carcinomas 5-year local control rates vary between 57% and 80% with larynx preservation rates of 73%–82% (Table 4). The TNM-related death rate is about 1%–4% for T1 carcinomas and 4%–9% for T2 carcinomas.

By comparison with transoral laser microsurgery, it becomes evident that primary radiotherapy is associated with on average lower local control rates, higher numbers of secondary laryngectomy, and substantially higher TNM-related deaths. Although routine post-treatment follow-up is generally performed for early detection of recurrences, the poorer results of primary radiotherapy are due to a much more difficult clinical assessment of the larynx after radiotherapy than after surgery. Radiotherapy

Table 4: Results of radiotherapy for T2 vocal cord carcinomas

Author	Number of patients	Local control	Larynx preservation	TNM related deaths	Mobility impaired
Dinshaw et al. 2000 [274]	216	57%	–	–	33%
Mendenhall et al. 2001 [37]	T2a: 146 T2b: 82	80% 72%	82% 76%	4% 4%	
Johansen et al. 2002 [276]	228	61%	74%	–	–
Jorgensen et al. 2002 [102]	234	67%	82%	–	–
Garden et al. 2003 [54]	230	72%	–	9%	50%
Cho et al. 2004 [277]	68	62%	–	–	–
Frata et al. 2005 [55]	256	73%	73%	–	27%
Groome et al. 2006 [278]	213	63%	–	–	–
Dagan et al. 2007 [282]	80	78%	80%	–	–
Smee et al. 2010 [280]	142	72%	–	15%	53%
Chera et al. 2010 [281]	T2a: 165 T2b: 95	80% 70%	81% 74%	– –	– –

cannot be repeated which limits therapeutic options in case of recurrence or a second primary tumor in the head and neck region. In most cases of local recurrence or residual tumor total laryngectomy is needed. About 11%–13% of patients treated with primary radiotherapy for early glottic cancer have to undergo secondary laryngectomy.

Thurnher et al. [52] published the only study comparing all three therapy options for early glottic carcinoma. Transoral laser microsurgery, open vertical partial laryngectomy and primary radiotherapy were performed on 3 different cohorts of patients T1 vocal cord cancer at the Vienna University Hospital. Primary radiotherapy had significantly lower local control rates and disease-specific survival rates than the two surgical approaches, with transoral laser microsurgery offering the best overall results.

2.7 Complications

The published literature demonstrates that complications after transoral laser microsurgery are rare and amount to less than 1%. Late complications do not occur. The complication rate of primary radiotherapy is also low. Severe complications such as chondronecrosis occur in less than 1% of T1 carcinomas treated with primary radiotherapy [37], [38], [40], [53]. Following radiotherapy of T2 carcinomas, complication rates between 2% and 4% have been reported [37], [54], [55].

2.8 Functional Results

There is consensus that since the introduction of transoral laser microsurgery for the treatment of early glottic cancer, the voice quality has improved compared to open cordectomy via laryngofissure [56]. Post-treatment voice quality was evaluated in a number of studies comparing transoral laser microsurgery with primary radiotherapy [57], [58]. Some of those studies found no difference in voice quality whereas others state better results after radiotherapy [59], [60].

Several recent studies comparing quality of voice after laser microsurgery and radiotherapy noted that despite different patient selection and methods of voice analysis (perceptive voice analysis, use of semi objective scales or quantitative acoustic measurements) similar voice results were achieved with both treatment methods [61], [57], [62], [63].

With the different methods of voice analysis, important parameters to assess voice quality objectively can be recorded. The objective voice quality and the self-perception of a voice handicap can differ significantly. The Voice Handicap Index (VHI) was developed to document the patient's self-perception of voice quality [24]. VHI analysis done by Nunez Batalla et al. [62] showed that patients with T1 vocal cord cancer perceived little negative impact on their voice after transoral laser microsurgery or radiotherapy. In addition to acoustic parameters and the VHI for self-assessment Loughran et al. [63] evaluated voice quality by using two other instruments, the Vocal Performance Questionnaire (VPQ) and the Voice Symptom Score (VoiSS). No significant differences between transoral laser microsurgery and radiotherapy were found.

In 2006, Cohen et al. [64] reported the results of a meta-analysis of 6 studies on voice-related quality of life in patients with T1 glottic cancer treated with primary radiotherapy or transoral laser microsurgery. The VHI scores of 208 patients after transoral laser microsurgery and of 91 patients after radiotherapy were similarly low, suggesting little influence of both treatment modalities on voice-related quality of life.

In our clinical experience, postoperative voice quality is influenced by several factors. Of particular importance are both location and superficial extension and the depth of tumor invasion. These parameters determine the minimum extent of an oncologically sound tumor resec-

tion. The postoperative voice quality depends on the safety margins the surgeon chooses and whether the resection includes the anterior commissure [7], [65], [66]. Finally, voice quality is determined by an individual wound healing process, which is associated with varying degrees of granulation tissue and postoperative scarring. Effective postoperative voice therapy is another important factor. The prospects of successful voice rehabilitation depend ultimately on what functionally important structures the surgeon was able to preserve. These prospects are most favorable when the voice can be rehabilitated at the level of glottic phonation [67].

2.9 Surgical Voice Rehabilitation

As mentioned above most patients are satisfied with their voice after transoral laser microsurgery. However, endolaryngeal cordectomy often does result in dysphonia due to glottic insufficiency because of loss of tissue or scar formation, reducing vocal ability. Postoperative dysphonia is characterized by breathiness, roughness, asthenicity (auditive impression of weakness, hypofunctional voice) or strain (auditive impression of excessive tension associated with phonation), leading to the patient's demand for further treatment. Voice therapy seems to be sufficient for most patients. In suited cases surgical voice rehabilitation might be considered. Voice rehabilitation surgery should not be performed earlier than 6–12 months after tumor resection in order to wait for the final result of scar formation. The goal of the operation is to medialize the vocal fold to close the glottic gap and therefore improve voice quality.

Superficial scars involve Reinke's space and the vocal ligament. The epithelium must be freed from the ligament and a pouch is created. After implantation of autologous fatty tissue the pouch is closed by sutures [68], [69], [70], [71], [72]. As with sulcus-vergeture management is difficult. Smaller defects due to partial cordectomy involving the vocal ligament and the vocalis muscle can be treated with medialization surgery. In most cases the surgery has to be combined with the injection of collagen or autologous fatty tissue [73]. In selected cases injectable materials (e.g. Polydimethylsiloxan, Vox Implant®) can be of use [74]. Bigger defects due to complete or extended cordectomy are often difficult to treat. Scars involving the perichondrium and the thyroid cartilage are difficult to detach without perforating the pouch in which a cartilage strut is positioned [73], [74], [75]. In cases of tumor resections including the perichondrium, laryngeal framework medialization may be unsuccessful. Those patients should receive voice therapy with the aim to train supraglottic voice production.

Anterior glottic webs are inevitable after resection of anterior commissure carcinomas. Thin and superficial webs often cause no or only mild dysphonia and do not need further treatment. However, extensive scarring may result in severe dysphonia and dyspnea. The exact thickness of the web can be determined by microlaryngoscopy combined with 0°-, 45°-, and 70° telescopes. Thin and small webs are excised with the CO2 laser. To prevent reformation of the web, the anterior commissure is treated locally with Mitomycin-C (1 mg/ml) to inhibit proliferation of fibroblasts [76], [77]. If extensive fibrin exsudation and granulation tissue formation are seen postoperatively, another microlaryngoscopy with removal of granulation tissue and re-application of Mitomycin-C is advisable after 2 weeks. Webs that extend to the subglottis or recurrent webs after resection and Mitomycin-C application can be successfully treated by endoscopic scar resection and fixation of a silicon sheet or keel in the anterior commissure as described by Lichtenberger [78].

2.10 Cost of Therapy

Due to increasing importance of economic aspects of different treatment modalities, several cost analyses have been performed. According to most analyses laser microsurgery costs less than radiotherapy [79], [80], [81]. Laser microsurgery may dominate radiotherapy from a cost-utility standpoint because lesser resources are needed for salvage treatment.

2.11 Conclusion

The comparison of treatment results of laser microsurgery and open vertical partial laryngectomy in early glottic cancer shows that local control and disease-specific survival do not differ. Transoral laser microsurgery has widely replaced open surgery due to less morbidity, better voice quality and lower cost. Accordingly, no articles on open surgery for early glottic cancer could be found in the English literature in the last 10 years.

Today, laser microsurgery is an established method not only for midcordal carcinomas but for all early glottic carcinomas. We do not regard involvement of the anterior commissure to be a contraindication for laser microsurgery because of comparable local control rates for both laser microsurgery and open vertical partial laryngectomy. With SCPL-CHP excellent local control rates are achieved, however, it comes with the price of a higher morbidity and often severe impairment of voice and swallowing function. The literature of the past 10 years revealed that SCPL-CHP is performed on selected patients in only a few centers around the world.

Comparing radiotherapy to surgical therapy with regard to local control, larynx preservation and disease-specific survival surgical treatment is superior. The voice outcomes after laser microsurgery and radiotherapy are comparable.

Even though a randomized study could not be completed, the current literature allows the conclusion that laser microsurgery is the method of choice – highly accepted by the patient – for the treatment of early glottic cancer with regard to oncologic, functional, and economic aspects.

3. Glottic Carcinomas with Impaired Mobility or Fixation of the Vocal Cord

3.1 Definition

T2 glottic carcinomas comprise a very heterogeneous group of tumors. Some tumors show supra- and/or subglottic tumor extension with normal vocal cord mobility, while others cause impaired vocal cord mobility and show considerable supra- and/or subglottic extension. The two groups differ markedly in their prognosis. T2 tumors with impaired vocal cord mobility are comparable to T3 tumors with vocal cord fixation with respect to local control and survival.

3.2 Special Diagnostic Aspects

Beside routine laryngoscopy for the assessment of morphology and vocal cord mobility, CT or MRI scans of larynx and neck should be done for preoperative staging. Extensive tumor infiltration into thyroid or cricoid cartilage or into the soft tissue of the neck is a contraindication for partial laryngectomy. While infiltration to the soft tissue of the neck is usually easily detected by imaging technology, the diagnosis of thyroid cartilage erosion can be a challenge. In a meta-analysis published by Yousem and Tufano [82] sensitivity and specificity of thyroid cartilage infiltration were estimated to be 92% and 79% for magnet resonance imaging and 64% and 89% for computed tomography.

3.3 Oncologic Results

3.3.1 Results of Transoral Laser Microsurgery

In 2001, Steiner's group reported the results of laser microsurgery for 167 glottic cancer patients with impaired vocal cord mobility (T2b) or fixation (T3) [28]. Ninety-seven patients were classified as pT2b(p)N0M0 and 70 patients as pT3(p)N0M0. Forty-five per cent of pT3 tumors showed fixation of the arytenoid cartilage. Adjuvant radiotherapy was performed in 10.3% of stage II and in 8.6% of stage III patients. The Kaplan-Meier 5-year local control rate was 74% for pT2b carcinomas and 68% for pT3 carcinomas. Secondary laryngectomy was carried out in 13.4% and 14.3%, respectively. The 5-year ultimate local control rate was 87% and the 5-year disease-specific survival rate was 62% in both groups.
Postoperative voice quality was satisfying in the majority of patients despite the extensive partial laryngeal resections. Speech intelligibility in the telephone test was more than 90% for both groups. One patient developed a glottic/subglottic stenosis and has a permanent tracheostoma. No tracheotomies were done together with the transoral laser resections of the primary tumors. Only 11% of the stage II patients and 44% of the stage III patients needed a nasogastric feeding tube for a median time period of 4 or 5 days, respectively; all the other patients didn't need tube feeding. All patients fully recovered and regained normal swallowing function. In summary, with primary laser microsurgery in 70% of patients with pT2b and pT3 carcinomas, long-term locoregional control with preservation of a functional larynx was achieved at an overall low morbidity.
Little data on results of laser microsurgery in more advanced glottic carcinomas are to be found in the current literature. Motta et al. [83] reported on 37 patients with T3 glottic carcinomas, they treated with laser microsurgery. Fifty-five per cent of patients developed locoregional recurrences and in 35% secondary laryngectomy had to be performed. Peretti et al. [84] published results of 11 patients with T3 glottic carcinomas treated with laser microsurgery. The local control rate was 71.6% and the larynx preservation rate 72.7%.
Hinni et al. [85] reported the results of 117 patients with advanced laryngeal carcinomas undergoing laser microsurgery. Seventy-five (64%) patients had supraglottic and 42 (36%) glottic carcinomas. Oncologic results were not stratified for the two laryngeal subsites. Eleven (9%) tumors were classified as pT2, 73 (62%) as pT3, and 33 (28%) as pT4. Unilateral or bilateral neck dissection was performed in 92 (79%) patients and 45 patients (34%) underwent adjuvant radiotherapy. Postoperative complications following surgery of the primary tumor occurred in 8.5% of patients and the perioperative mortality rate was 3%. The Kaplan-Meier 5-year laryngeal preservation rate was 86%. The 5-year overall survival rate was 55% and the 5-year disease-free survival 58%. At the time of the last follow up examination, 2 of 68 (3%) survivors had a tracheostoma and 5 (7%) were dependent on a feeding tube. A similar study was published by Vilaseca et al. [86] including 147 patients with T3 laryngeal cancer (96 supraglottic and 51 glottic lesions). Unilateral or bilateral neck dissection was performed in 66.4% of patients and 17% were subjected to adjuvant radiotherapy. The Kaplan-Meier 5-year larynx preservation rate was 76.6% for supraglottic and 58.9% for glottic tumors. In a multivariate analysis the parameter "fixation of the vocal cord" was shown to be a negative predictor for preservation of the larynx and its function.

3.3.2 Results of Open Vertical Partial Laryngectomy

Local control rates estimate to 52%–76% in patients with glottic carcinomas with impaired vocal cord mobility treated with open vertical partial laryngectomy [41], [87]. Total laryngectomy is frequently indicated in glottic carcinomas with vocal cord fixation. A few selected cases are managed by hemilaryngectomy. In those patients the local control rates average between 73% and 83% after partial laryngectomy [88], [89], [90], [91]. Patients treated with primary laryngectomy and bilateral neck dissection with or without adjuvant radiotherapy reached local control rates of 69%–87%, 5-year overall survival rates of

53%–56%, and a disease-specific survival rate of 71%–78% [92], [93], [94].

3.3.3 Results of Supracricoid Partial Laryngectomy

Another organ-preserving treatment option for glottic tumors with impaired vocal cord mobility or vocal cord fixation is the supracricoid partial laryngectomy with cricohyoidoepiglottopexy (SCPL-CHEP), without [95], [96] or with neoadjuvant chemotherapy with cisplatin and 5-fluorouracil [97], [98], [99]. As contraindications for this procedure are generally regarded fixation of the arytenoid cartilage, subglottic tumor extension to the upper border of the cricoid cartilage, infiltration of the cricoid cartilage or thyroid cartilage, extensive infiltration of the preepiglottic space, and extralaryngeal tumor spread [100].

Laccourreye et al. [99] reported in 1999 on 100 patients with T2 glottic carcinomas treated with SCPL-CHEP. Vocal cord mobility was impaired preoperatively in 54% of patients. The anterior commissure was involved in 42% of cases, and there was involvement of the infraglottic region in 10%. Patients received three cycles of neoadjuvant chemotherapy with cisplatin and 5-fluorouracil at intervals of 15–21 days. Complete remission was achieved in 24% of patients and partial remission in 58%. The 5-year local control rate was 97.7% for T2a and 93.8% for T2b carcinomas. The larynx was preserved in 95% of patients. Nine per cent of patients suffered from postoperative aspiration pneumonia; one patient had a total laryngectomy for functional failure. Using the same treatment regimen for glottic carcinoma with vocal cord fixation in 20 patients, Laccourreye and his group achieved a 3-year local control rate of 89.2% and a larynx preservation rate of 90% [97]. Chevalier et al. [96] reported similar results in 112 patients with glottic carcinoma with impaired vocal cord mobility (n=90) or vocal cord fixation (n=22) without the use of neoadjuvant chemotherapy. The 5-year local control rate was 97.3% and the 5-year larynx preservation rate 95.5%.

In another study by Laccourreye's group, Dufour et al. [101] reported on the oncologic results of 118 patients with "endolaryngeal" carcinomas classified as T3 who were treated with SCPL. In 66 (56%) patients supraglottic carcinomas, in 43 (36%) patients glottic carcinomas, and in 9 (8%) transglottic carcinomas were diagnosed. Onehundred (85%) patients received 2–6 cycles of neoadjuvant chemotherapy with cisplatin and 5-fluorouracil. Ninety-nine (84%) patients underwent uni- or bilateral neck dissection and 24 (20%) patients had adjuvant radiotherapy. In 106 of 118 (89.8%) cases a functional larynx could be preserved. In course of follow up 63 (53%) patients deceased. In 30% the cause of death was a second primary tumor and 27% deceased due to intercurrent diseases. Data on therapy-related complications and mortality are not reported.

3.3.4 Results of Radiotherapy

Local control rates after primary radiotherapy of T2 glottic carcinoma with impaired vocal cord mobility average between 60% and 76%, and the rate of larynx preservation between 70%–80% [102], [103], [104], [105], [106], [107], [108]. Fein et al. [105] achieved a 5-year local control rate of 87% for T2 glottic carcinomas with normal vocal cord mobility. This rate declined to 76% when vocal cord mobility was impaired. 5-year local control rates of 30%–68% are reported for primary radiotherapy of T3 glottic carcinomas, with definitive local control rates of 80%–86%. The 5-year overall survival rate is 51%–59%. The 5-year larynx preservation rate is 60%–76% [102], [109], [110], [111].

Two studies were highly influential on the treatment of advanced laryngeal carcinomas, particularly in the USA. One of these studies was conducted by the Department of Veterans Affairs Laryngeal Cancer Study Group in 1991 [112]. Two groups of selected patients with laryngeal carcinomas were compared. One group was treated with induction chemotherapy followed by radiotherapy; the other one underwent primary laryngectomy and adjuvant radiotherapy. Comparing the survival rates of these groups only minimal differences could be found.

A second study published by the Radiation Therapy Oncology Group (RTOG) 91-11 study in 2003 [113] came to the conclusion that simultaneous chemoradiotherapy is superior to sequential chemoradiotherapy or radiotherapy alone. Included in this study were T2, T3, and "low volume" T4 carcinomas. The authors conclude that simultaneous chemoradiotherapy can be regarded standard treatment for patients demanding an organ-preserving approach under the prerequisite, that the tumor treated corresponds to the inclusion criteria of the study. In the authors' opinion, primary non-surgical treatment is feasible for the majority of patients and total laryngectomy should strictly be reserved to "salvage surgery".

Critical analysis of the data could show that both studies had included predominately patients with supraglottic carcinomas, 61% in the VA-study and 68% in the RTOG 91-11-study. In addition, 48% patients in the VA-study and 42% of in the RTOG 91-11-study had mobile vocal cords. These patients could have just as well been treated with a partial laryngectomy. Since both studies included patients with intact vocal cord mobility a conclusion on treatment results of primary chemotherapy in patients with vocal cord fixation can not be drawn. A French study by the GETTEC (Groupement d'Etudes des Tumeurs de la Tête et du Cou), comparing induction chemotherapy followed by radiotherapy with surgery and postoperative radiation in patients with laryngeal carcinomas with vocal cord fixation had to be terminated due to significantly poorer results of chemoradiotherapy [114]. In another study on the feasibility of larynx preservation, 104 larynx cancer patients were treated with induction chemotherapy followed by radiotherapy which resulted in a 31% 5-year laryngeal preservation rate [115].

Even though more than 80% of the patients in the VA- and RTOG-study, respectively, had a Karnofsky index of >90 only 70% of patients could complete the entire chemoradiation protocol due to toxicity. Eighty-two per cent of patients suffered from grade 3 and 4 toxicity, 5% died due to therapy-related complications. In summary, therapy-related mortality is significantly higher when organ-preservation protocols are used than after primary surgical treatment.

Caused by the results of those two studies, many oncology centers especially in the United States treated their patients with advanced laryngeal carcinomas with simultaneous chemoradiotherapy in the hope of organ preservation. In 2006, Hoffmann et al. [116] stated for the first time, that survival rates for carcinomas of all locations had increased during the last two decades except for cancer of the larynx. In particular remarkable is the observation that survival rates decreased in patients with advanced laryngeal carcinomas, early supraglottic carcinomas, and supraglottic carcinomas classified as T3N0M0. Moreover among all patients with laryngeal carcinomas, classified T3N0M0, regardless of the tumor location, the best survival rate (65.2%) was documented after primary surgery and adjuvant radiotherapy. In 2007, Chen and Halpern [117] analyzed data collected by the National Hospital-Based Cancer Registry. The data base comprises 7,019 cases. They found that the risk of death was significantly higher in T3 larynx cancer patients after chemoradiation than after laryngectomy alone.

Recently, a more critical assessment developed and has challenged the concept of larynx preservation by various chemoradiation protocols, due to a significant number of late complications, functional impairments and locoregional recurrences [118], [119].

3.4 Conclusion

The role of laser microsurgery in the treatment of laryngeal carcinomas with vocal cord impairment or fixation cannot yet be definitively assessed on the basis of the current literature. Nevertheless, results published to date indicate that approximately 70% of patients with pT2b and pT3 carcinomas remain free of local tumor recurrence after primary laser surgery, with minimal morbidity and a functional larynx. Results of laser microsurgery for T4 glottic carcinomas cannot be considered because adequate data are not yet available.

Comparing the results of vertical partial laryngectomy to laser microsurgery is difficult because patients are selected for partial laryngectomy on an individual basis and total laryngectomy may already be indicated in patients with T2b and T3 tumors. The local control rates achieved with supracricoid partial laryngectomy are excellent. It should be noted, however, that the patients were selected according to the criteria stated. Due to the surgical procedure itself (and due to prior induction chemotherapy applied in many cases), morbidity is high. This is the reason, why supracricoid partial laryngectomy is not an option for all patients.

The results of the studies, investigating the feasibility of larynx preservation with induction chemotherapy followed by radiotherapy or with simultaneous chemoradiation in selected patients, show that this concept cannot be regarded as standard treatment presently. The fact that a decrease in survival rates parallels the increase in popularity of organ-preserving chemoradiation seems worrisome.

4. Supraglottic Carcinomas

4.1 Definition

Early supraglottic carcinomas are defined as tumors not infiltrating the preepiglottic fat, not immobilizing a vocal cord, and not metastasizing to lymph nodes of the neck. Supraglottic carcinomas with vocal cord fixation and/or invasion of the preepiglottic fat, the postcricoid region and/or with erosion of the inner cortex of the thyroid cartilage are classified as T3 tumors. Surgical treatment options for supraglottic carcinomas comprise open supraglottic laryngectomy, transoral laser microsurgery, and supracricoid partial laryngectomy with cricohyoidopexy.

4.2 Open Supraglottic Laryngectomy

Supraglottic laryngectomy was first described by JM Alonso in 1947 [120]. The procedure consists of a resection of the entire supraglottis such as the epiglottis, the preepiglottic fat, and the ventricular folds together with the supraglottic part of the thyroid cartilage. Contraindications are tumors involving the glottis, the floor of the ventricles, infiltrating the thyroid cartilage, the base of the tongue extensively, and impair vocal cord mobility. With regard to these requirements open supraglottic laryngectomy can be indicated for T1, T2, and for selected T3 carcinomas.

The procedure starts with a U-shaped skin incision. The skin flap is elevated in the subplatysmal plane, followed by a tracheostomy. After a bilateral (selective) neck dissection the infrahyoid muscles are dissected from the hyoid bone and rotated caudally. An incision is made through the external perichondrium of the thyroid cartilage and the perichondrium is carefully dissected from the cartilage down to the vocal cord plane and the superior cornu of the thyroid cartilage is exposed. The thyroid cartilage is then transected horizontally. The pharynx is opened in the vallecula and the larynx exposed. Both aryepiglottic folds are transected and the incision follows the floor of the ventricles above the anterior commissure. The hyoid bone or if resected the base of the tongue is sutured with the laryngeal remnant for closure. Then the perichondrial flap is sutured to the hyoid bone and the infrahyoid muscles are sutured superiorly. In advanced tumors the resection can be extended to the base of the tongue or one arytenoid cartilage.

The supracricoid partial laryngectomy with cricohyoidopexie (SCPL-CHP) was first described by Labayle [121]. The indication for this procedure comprises supraglottic tumors with limited infiltration of the preepiglottic fat, limited erosion of the thyroid cartilage and tumors with fixation of one vocal cord but without fixation of the arytenoid cartilage. This operation was used for surgical treatment of T1, T2 and selected T3 and T4 supraglottic tumors.

After elevating the skin flap, tracheostomy, and neck dissection the strap muscles are divided in the midline. The thyrohyoid muscle and the sternohyoid muscle are dissected from the hyoid bone. The thyroid cartilage is skeletonized and the constrictor pharyngis muscle released from the cartilage. The larynx is opened in the vallecula and the incision made anterior to the arytenoids cartilage and the superior border of the cricoid cartilage is dissected. Both vocal folds, ventricular folds, epiglottis, and preepiglottic fat are removed together with the thyroid cartilage. Closure is performed by impaction of the cricoid cartilage to the hyoid bone. The strap muscles are then sutured and the skin flap is closed.

Vaughan from Boston [122] was the first surgeon describing a supraglottic partial laryngectomy carried out transorally with a carbon dioxide laser. Since 1979 Steiner used the carbon dioxide laser for transoral endoscopic surgery of selected supraglottic carcinomas [123], [124]. In 1983, Davis et al. [125] reported on a first series of 20 patients with benign bulky lesions obstructing the airway or small suprahyoid carcinomas of the epiglottis that were treated with laser epiglottectomy. Later Davis et al. [126] and Zeitels et al. [127] published the results of laser microsurgery in selected patients with supraglottic carcinomas. T1 and T2 as well as selected T3 and T4 carcinomas were resected with this method.

The rare small carcinomas of the suprahyoid epiglottis or ventricular fold can usually be easily exposed and excised en bloc. Carcinomas of the infrahyoid epiglottis are exposed with a bivalved laryngoscope and are best removed piecemeal by making an incision in the vallecula glossoepiglottica and splitting the epiglottis in the midline, resecting the preepiglottic fat while preserving the vocal folds and arytenoid cartilages (Figure 5, Figure 6). Tumor that has spread along the inner surface of the thyroid cartilage and infiltrates the muscle tissue in the paraglottic space on the glottic level can be removed along with parts of the vocalis muscle. With advanced tumors, parts of the base of the tongue, piriform sinus or one arytenoid cartilage can be included in the resection [3] (Figure 7). The extent of laser resection is limited by the patient's ability to regain adequate swallowing function. To prevent postoperative bleeding the superior laryngeal artery should be identified and liger clipped (Figure 8). Tracheostomy is generally unnecessary due to very limited postoperative edema, even after extensive supraglottic laser resections. A tracheotomy should be considered in elderly patients with significantly impaired pulmonary function, in patients with a bleeding diathesis (e.g., anticoagulant medication, hemodialysis), or if heavy bleeding occurred during surgery.

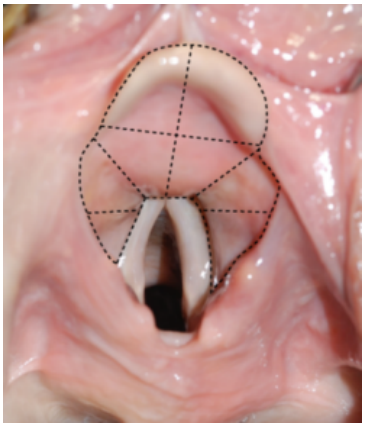

Figure 5: Anatomic specimen, non-fixed. The dotted lines show the resection in case of a supraglottic carcinoma.

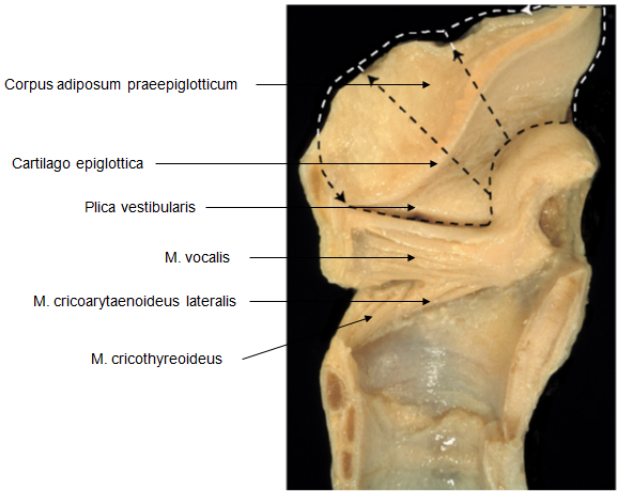

Figure 6: Right adult hemilarynx. Specimen of the scientific collection of the Inst. of Anatomy of CAU Kiel. Photograph: B. Tillmann. The dotted lines show the resection in a case of a supraglottic carcinoma with complete resection of the epiglottis, the preepiglottic fat and the false cord.

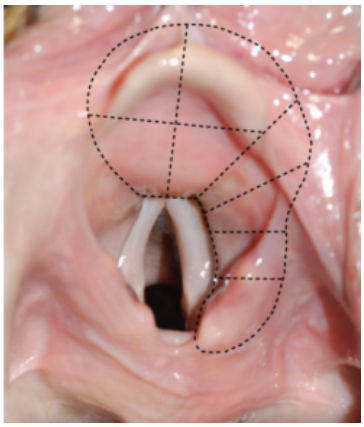

Figure 7: Anatomic specimen, non-fixed. The dotted lines show the resection in a case of an advanced supraglottic carcinoma with the resection extended to the aryepiglottic fold and the arytenoid cartilage.

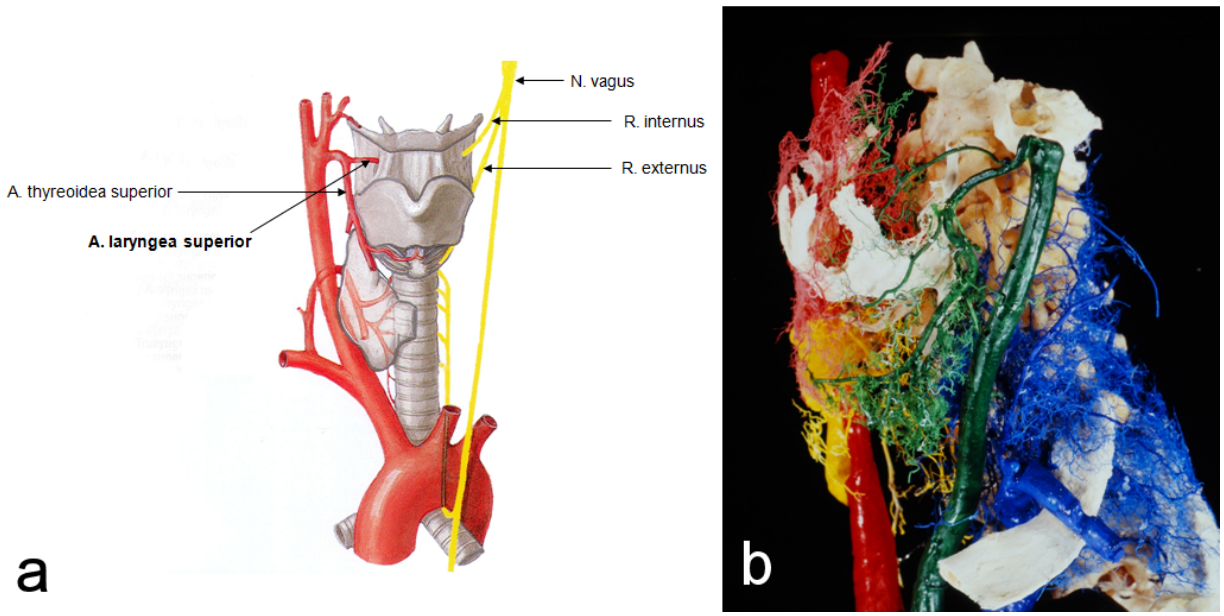

Figure 8: a: Diagram showing arteries and nerves of the larynx. From B. Tillmann, 2010 [262]. b: Corrosion specimen of the arteries of the neck. Four-colour injection of methacrylat with preservation of the laryngeal skeleton. Specimen of the scientific collection of the Inst. of Anatomy of CAU Kiel. Klaws fecit, Photograph: B. Tillmann.

4.2.1 Special Aspects of Histopathologic Examination

As a rule most supraglottic carcinomas are resected in multiple blocks. Marking the specimens precisely is essential for an adequate orientation for histopathologic examination [5]. No matter which surgical methods (open surgery or laser microsurgery) are being used, tumor free resection margins must be achieved to prevent tumor recurrence. Prades et al. [128] reported in a series of 110 patients in 23% of cases microscopic positive resection margins after open supraglottic laryngectomy. The risk for a local tumor recurrence was 4 times higher in these patients despite adjuvant radiotherapy. Iro et al. [129] pointed out that favorable oncologic results in transoral laser supraglottic resections could only be achieved with tumor free resection margins (R0 resection). In case tumor free resection margins can not be achieved they recommend transoral laser re-resection or open supraglottic laryngectomy, alternatively total laryngectomy. Adjuvant radiotherapy did not prove efficacy in the R1 and R2 situation and was therefore not recommended.

Blanch et al. [130] analyzed the prognostic implications of positive resection margins in 357 patients with laser micro surgically resected tumors of the larynx and pharynx. They could show that positive resection margins were associated with higher rates of local recurrences, distant metastases, loss of organ, and poorer survival. These results acknowledge the importance of re-resection if tumor-free surgical margins are not achieved after the first surgery. Jäckel et al. [131] examined the prognostic relevance of positive margins in 1,467 patients treated laser microsurgically because of tumors in various sites of the upper aerodigestive tract. The authors could show that the prognosis did not worsen when tumor-free surgical margins were achieved by re-resection. The risk for a local recurrence was higher in patients with residual tumor in the re-resection specimen. In those cases another re-resection was advocated.

4.2.2 Classification of Endoscopic Supraglottic Laryngectomy

In 2009, Remacle et al [132] published on behalf of the European Laryngological Society a proposal for the classification of endoscopic supraglottic laryngectomy. According to the extent of resection, supraglottic partial resections are classified in seven types. If this complex classification system will be incorporated into clinical practice is still undecided.

4.3 Complications

The complication rate is a major concern when evaluating a therapeutic procedure. The most common complications after open supraglottic laryngectomy are postoperative endolaryngeal hemorrhage, pharyngocutaneous fistula, and supraglottic stenosis. The incidence of postoperative hemorrhage is about equal for open supraglottic laryngectomy, SCPL-CHP, and laser microsurgery with an average between 3%–14% in different studies [133], [134], [135], [136], [137]. However, every postoperative bleeding after endoscopic surgery in a non-tracheotomized patient is a serious and potentially life-threatening complication due to the risk of aspiration of blood [138]. Nevertheless, bleeding from the base of tongue or the laryngeal remnant with fatal outcome has been described after open supraglottic laryngectomy [139], [140]. An up to 18% rate of surgical complications has been reported after SCPL-CHP [141], [142].

The risk of postoperative pulmonary complications after SCPL increases with age and pre-existing pulmonary disease. This explains why patients older than 60 years of age normally do not qualify for CHP [143].
Laryngeal stenosis occurs less often after endoscopic supraglottic resection than after open supraglottic laryngectomy or SCPL-CHP. The incidence is reported 0%–10% after laser supraglottic resection and 5%–15% after open supraglottic laryngectomy [136], [137], [144].
The most prevalent complications after primary radiotherapy are chondronecrosis and the airway obstructing laryngeal edema. The incidence of severe complications amounts to 2%–7% [145], [146], [147]. In 1.5% to 2% of patients secondary laryngectomy is required after irradiation of a supraglottic carcinoma due to chondronecrosis or persistent laryngeal edema. Another 0.6%–2.5% of patients need a permanent tracheostoma [145], [146], [147].
Adjuvant radiotherapy is not indicated in patients with complete removal of the primary tumor and histopathologically tumor-free cervical lymph nodes. Adjuvant radiotherapy is indicated in cases where microscopic residual tumor is assumed to be present at the primary tumor site (R1 resection), in patients with more than one tumor positive lymph node in the neck and in patients with lymph node metastases with extracapsular spread. Whether postoperative radiotherapy after supraglottic laryngectomy has an adverse effect on laryngeal function is controversial. Steininger et al. [148] found that patients receiving postoperative irradiation were more likely to need lifelong PEG tube feeding and were also more likely to have airway obstruction due to edema. Other studies found no increase in complication rates following adjuvant radiotherapy [149], [150]. It is reasonable to assume, however, that the complication rate increases when doses higher than 50 Gy are applied to the larynx [150], [151].

4.4 Oncologic Results

4.4.1 Results of Open Supraglottic Laryngectomy

The oncologic results of open supraglottic laryngectomy in early supraglottic carcinomas are excellent. The local control rate is between 90%-100% for T1 tumors and 80%-97% for T2 tumors [152], [153], [154], [155], [156], [157], [158], [159], [160], [161], [162].
In the recent literature (since the year 2000) only a few articles are found on open supraglottic laryngectomy. Prades et al. [128] report on 110 patients with T1-T3 supraglottic carcinomas. The local control rate was 90.3% and the 5-year overall survival rate 52%. Similar results were published by Bron et al. [163] for 75 patients with T1-T3 supraglottic carcinomas. In this series, the 5-year local control rate was 92.5%, the organ preservation rate was 98.5%, and the 5-year overall survival rate was 75%. A retrospective analysis of 267 patients (187 T1/T2-carcinomas, 80 T3/T4-carcinomas) done by Sevilla et al. [164] showed also comparable results. In this study the local control rate was 92% and the larynx could be preserved in 82% of patients. The 5-year disease-specific survival rate was 92% for stage I and 71% for stage II. Fifteen per cent of patients needed a permanent tracheostoma and 9% had to undergo secondary laryngectomy due to functional reasons.
The local control rates achieved for T3 carcinomas with classic or extended open supraglottic laryngectomy range from 71% to 94% [157], [165], [166], [167].

4.4.2 Results of Supracricoid Partial Laryngectomy

SCPL-CHP can be performed in carcinomas with infiltration of the ventricle or the paraglottic space (T2 or T3 tumors). Schwaab et al. [142] report on 146 patients mostly with T2 and T3 carcinomas who underwent SCPL-CHP. The local control rate was very good, with only 4% developing local recurrence. In 19% clinically relevant aspiration was noticed postoperatively and 9% had to be laryngectomized due to intractable aspiration. The larynx could be preserved in 85% of patients. The 5-year overall survival rate was 88%.
The local recurrence rate after SCLP-CHP is also very low in other series, ranging from 0% to 7% [43], [168], [169], [170]. It should be noted, however, that most of the tumors treated with SCLP-CHP were T2 and T3 carcinomas with “minimal infiltration” of the preepiglottic space, tumors involving the paraglottic space or vocal cords, or tumors classified as T4 lesions with only “minimal” infiltration of the thyroid cartilage [142], [168], [169].

4.4.3 Results of Laser Microsurgery

While laser microsurgery is used increasingly in the treatment of glottic carcinomas, only few reports have been published on the endoscopic resection of supraglottic carcinomas. Steiner [25] and Eckel and Thumfart [171] reported respectively on 30 and 15 patients with supraglottic carcinomas. Zeitels et al. [172] analyzed the results of laser microsurgery in 42 patients with supraglottic carcinomas in a multi-institutional study. Nineteen patients with T1 or T2 tumors treated with laser microsurgery alone were cured. Of 23 patients, mostly with T2 tumors, who received both surgery and postoperative irradiation, 4 developed local recurrences and were salvaged by total laryngectomy. In 1997, Eckel [173] reported the results of supraglottic laser resection in 46 patients with T1 and T2 tumors. Four (8.7%) patients developed local or locoregional recurrences, 5 (10.9%) required secondary laryngectomy due to functional reasons. Iro et al. [129] reported in 1998 on transoral supraglottic laser resections in 141 patients with the following UICC stage distribution: stage I, 23.4%; stage II, 25.5%; stage III, 16.3%; and stage IV, 34.8%.
In 1999, Rudert et al. [135] reviewed the results of transoral laser microsurgery in 34 patients with T1-T4 tumors, 12 of whom were treated with palliative intent. None of the patients who underwent the surgery

for attempted cure developed local recurrence. The 3-year overall survival rate for stages I and II disease was 88%. Ambrosch et al. [134] performed laser microsurgery in 48 patients with supraglottic T1 and T2 carcinomas. The 5-year local control rate was 100% for pT1 tumors and 89% for pT2 tumors. None of the patients required secondary laryngectomy for tumor recurrence or functional reasons. The 5-year recurrence-free survival rate in this series was 83%, and the 5-year overall survival rate was 76%.

Since 2000 a series of studies have been published about therapy results of transoral supraglottic laryngectomy. Grant et al. [174] reported on behalf of the Mayo-group on 38 patients with supraglottic carcinomas (T1/T2 22 patients, T3/T4 16 patients). The 2-year local control rate was 97%. In 79% of the patients a functional larynx could be preserved. Remarkably, the majority of patients (20 out of 38) received a tracheostomy due to various reasons. Agrawal et al. [175] published a prospective phase 2-study for the Southwest Oncology Group in which 34 patients with supraglottic carcinomas were included (T1 7 patients, T2 27 patients). According to the study protocol, laser microsurgical supraglottic laryngectomy followed by radiotherapy was performed in all patients. Only one patient developed a local recurrence and had to undergo total laryngectomy. Nine per cent of the patients suffered persistently from severe swallowing impairment. It has to be noted that a combined treatment protocol for early supraglottic carcinoma is an overtreatment for those tumors. As to be expected, patients demonstrated good local control but with a substantial number of functional failures. Bumber et al. [176] treated 64 patients with supraglottic carcinomas (T1 29 patients, T2 35 patients) with transoral laser resections. Two patients developed a local recurrence and needed total laryngectomy. Another patient had to undergo total laryngectomy due to functional reasons. The 5-year recurrence-free survival rate was 93%.

Two recent studies compare open supraglottic laryngectomy with transoral laser microsurgery. Bussu et al. [177] compare 78 patients treated with open surgery with 70 patients undergoing endoscopic supraglottic laryngectomy. While organ preservation rate and survival rate showed no statistically significant difference, the functional results were distinctively better after laser microsurgery. Karatzanis et al. [178] describe 101 patients with T1-T2N0 supraglottic carcinomas undergoing transoral laser microsurgery (n=49), open supraglottic laryngectomy (n=29), or total laryngectomy (n=23). Comparing local control rates and disease-specific survival rates of the three groups, no statistically significant difference was noted. Even though not statistically significant, there was a trend towards better functional outcome in the transoral laser microsurgery group. Those patients had less complications and fewer permanent tracheostomies and PEG tubes than patients after open supraglottic laryngectomy.

There are few reports on laser surgery for supraglottic T3 carcinomas in the literature. Rudert et al. [135] report results in 9 patients with T3 carcinomas (4 treated with palliative intent) and 8 patients with T4 carcinomas (5 treated with palliative intent). Two of 9 patients (22%) with T3 tumors and 5 of 9 patients (63%) with T4 tumors developed local recurrences. In the series of Iro et al. [129], a local recurrence was diagnosed in 5 of 15 patients (33%) with T3 carcinomas and in 3 of 33 patients (9%) with T4 carcinomas. While Rudert et al. [135] state that supraglottic carcinomas with invasion of the preepiglottic fat are endoscopically resectable, Iro et al. [129] advise restraint in treating T3 tumors with transoral laser surgery.

Ambrosch et al. [28] treated 50 patients with pT3 supraglottic laryngeal carcinomas (40 stage III, 10 stage IV) with transoral laser microsurgery. In 41 (82%) patients, the tumor was classified pT3 due to invasion of the preepiglottic fat; in 9 (18%) patients vocal cord fixation was present preoperatively. In 13 (26%) patients invasion of the paraglottic space and in 9 (18%) cases superficial tumor spread to one or both vocal cords was diagnosed. These patients were treated with laser microsurgery as an alternative to extended supraglottic laryngectomy, SCPL-CHP, or total laryngectomy. The 5-year local control rate was 86%. Four per cent of the patients underwent total laryngectomy due to local tumor recurrence. The 5-year recurrence-free survival rate was 71%. All patients had good vocal function. One patient developed a supraglottic stenosis after surgery followed by adjuvant radiotherapy and required a permanent tracheostoma. All patients were on an unrestricted oral diet after removal of the feeding tube. Special swallowing training was not required. None of the patients needed total laryngectomy for functional reasons.

Motta et al. [179] achieved a local control rate of 77% and an overall survival rate of 81% in 18 T3 supraglottic cancer patients treated with laser microsurgery. Peretti et al. [180] reported on a series of 80 patients treated with laser microsurgery in which 20 patients with pT3 lesions showing “limited infiltration” of the preepiglottic fat. In 88.2% of patients larynx preservation was achieved, the 5-year disease-free survival was 59.6%.

Based on the current literature it can be concluded that laser microsurgery is an alternative to open supraglottic laryngectomy. Although local recurrence rates are slightly higher with laser microsurgery, survival rates are comparable. Laser microsurgery, open supraglottic laryngectomy, and SCLP-CHP show similar results with regard to larynx preservation. This is due to higher secondary laryngectomy rates, reported in some series above all after SCPL-CHP, due to intractable aspiration.

4.4.4 Results of Radiotherapy

With primary radiotherapy supraglottic T1 carcinomas can be locally controlled in 75%-100% and T2 carcinomas in 62%–83% of cases [181], [182], [183], [184], [185], [186], [187]. While Inoue et al. [185] obtained significantly better local control rates for tumors of the epilarynx than for tumors of the infrahyoid epiglottis, other authors

did not find differences in local control rates for different subsites of the supraglottis [184], [188]. A significant predictor for local control, however, is the tumor volume determined by computed tomography [189].

Published data show that patients whose tumors could have been treated with voice preserving partial laryngectomy will usually require total laryngectomy in case of recurrence after primary radiation therapy. Johansen et al. [190] treated 117 patients with early supraglottic carcinomas with primary radiotherapy; 31% of patients required a total laryngectomy because of tumor recurrence. In the cohorts of Inoue et al. [185], Mendenhall et al. [186], and Johansen et al. [191] 17%, 14%, and 27% of patients, respectively, had to undergo salvage laryngectomy.

In supraglottic T3 carcinomas local control rates of 50%–76% can be achieved with primary radiotherapy [145], [146], [147], [181], [191]. Hinerman et al. [147] were able to preserve the larynx in 68% of their patients treated with radiotherapy for supraglottic T3 carcinomas and Nakfoor et al. [145] in 72%. In the series done by Johansen et al. [191], 36% (31 out of 87) of supraglottic T3 carcinoma patients treated with primary radiotherapy had to undergo salvage laryngectomy. The following survival rates have been reported: the corrected 5-year survival rate was 53% in the series of Sykes et al. [146], the 5-year recurrence-free survival rate was 76% in the series of Nakfoor et al. [145], and the 5-year disease-specific survival rate for stage III carcinomas was 81% in the series of Hinerman et al. [147].

The results of studies investigating the efficacy of chemoradiation protocols for larynx preservation [112], [113] have been discussed in the "glottic carcinoma" section.

4.5 Functional Results

All authors who have reported on the transoral laser resection of supraglottic carcinomas agree that swallowing rehabilitation proceeds more quickly and has better outcomes than open supraglottic laryngectomy. The rate of secondary laryngectomy for persistent aspiration after open supraglottic laryngectomy is in the range of 3.5%–12.5% [128], [149], [152], [164]. The incidence of postoperative aspiration and the time needed for swallowing rehabilitation varies with age, general health condition, and with the extent of resection of the base of tongue and arytenoid cartilage [133], [192], [193]. Due to considerable morbidity and postoperative functional impairment, open supraglottic laryngectomy often does not qualify as a treatment option, particularly in elderly patients with pre-existing pulmonary disease.

On the whole, the functional results of laser microsurgery for supraglottic T1-T3 carcinomas are very favorable. Patients need nasogastric tube feeding normally for a few postoperative days. Aspiration is minimal and occurs in the early postoperative period only and there is a reduced need for secondary tracheostomy and laryngectomy due to aspiration problems [28], [129], [134], [137], [178], [194], [195].

Mechanisms contributing significantly to the recovery of swallowing function after supraglottic, either open or endoscopic laryngectomy are: the oropharyngeal transit time of the bolus, closure of the airway at the laryngeal entrance, the position of the laryngeal remnant in relation to the base of the tongue, and the movement of the base of the tongue toward the posterior pharyngeal wall [193], [196], [197]. Patients who regain these functions postoperatively meet the prerequisites for a normal swallowing function.

We attribute the early and consistently successful swallowing rehabilitation in the patients treated by us to a variety of factors. The avoidance of tracheotomy, the integrity of the base of the tongue and pharyngeal muscles and the preservation of the hyoid bone with the supra- and infrahyoid muscles, enable the larynx to move normally during deglutition. At least one mobile arytenoid cartilage was preserved in all operations, to enable functional closure of the larynx. We also believe that preserving the extralaryngeal portions of the superior laryngeal nerves is an important factor in sensory reinnervation.

In most patients undergoing a supracricoid partial laryngectomy, the feeding tube can be removed within a month after surgery. But the patients will require 6–12 months to return to their normal eating habits [43], [45], [170], [198]. Approximately one third of patients will have to accept permanent limitations [45], [198]. SCPL also causes an inevitable change in voice quality, which can adversely affect the quality of live, especially in female patients [45].

4.6 Conclusion

As for early glottic carcinomas, there are little data found on open surgery for early supraglottic carcinomas in recent literature. The results of laser microsurgery in patients with T1-T3 supraglottic cancer are comparable to those of open supraglottic laryngectomy with regard to local control and survival rates. Transoral microsurgery makes it possible to preserve functionally important structures, thereby reducing alterations in the mobility of the laryngeal remnant and pharynx thus facilitating earlier and better swallowing. With the low postoperative morbidity of laser microsurgery, curative surgical treatment can be offered to patients who would not have been considered candidates for open supraglottic laryngectomy. The results of transoral microsurgery and open supraglottic laryngectomy are somewhat better than the results published for primary radiotherapy with regard to local control and survival, and they are superior with respect to organ preservation.

On the basis of current data, the concept of induction chemotherapy followed by radiotherapy or simultaneous chemoradiation with the aim of larynx preservation cannot be regarded as standard treatment at the present time.

5. Carcinomas of the Hypopharynx

5.1 Preliminary Remarks

Hypopharyngeal carcinoma has the poorest prognosis among all carcinomas of the upper aerodigestive tract. This is due mainly to a high rate of local tumor recurrences, a high prevalence of cervical lymph node metastasis at the time of diagnosis, a high rate of syn- and metachronous distant metastases and second primary tumors, and a high rate of alcohol and tobacco consumption and consumption-related diseases.

The National Cancer Data Base Report of the year 1997, to this day the report with the largest data on carcinomas of the hypopharynx, indicates a 5-year disease-specific survival rate of 31.4% in 3,906 cases of hypopharyngeal carcinoma and a 33.6% survival rate in 822 cases of carcinomas of the piriform sinus [199], [200]. Regardless of treatment, the 5-year disease-specific survival rate in the cohort of 1,295 patients treated between 1980 and 1985 was 63% for stage I, 58% for stage II, 42% for stage III, and 22% for stage IV disease. Further analysis of the data showed that patients with early-stage disease treated with radiotherapy alone had lower survival rates than patients who received primary surgical treatment, with or without adjuvant radiotherapy. In advanced stage disease, cancers treated with radiotherapy alone had the poorest survival rates. In addition, the data clarified that 44% of hypopharynx cancer patients were treated with a combined treatment consisting of surgery and radiotherapy. With regard to surgical procedures, total laryngopharyngectomy was performed in 57.5% of cases and partial laryngopharyngectomy or other partial resections in 25.3% of cases. Only 4% of patients underwent laser resection. Severe treatment-related complications occurred in 6–34% of cases, and fatal complications were observed in 2.4%–14% [199].

Recent literature shows that the advances in imaging technology, radiotherapy, chemotherapy, surgery, and multimodality treatment protocols have not led to a reduction in mortality. Regarding different therapy concepts for stage I and II hypopharyngeal carcinomas, the 5-year survival rate averages between 52% and 77% for radiotherapy (with or without concomitant chemotherapy) [201], [202], [203], [204], between 56% and 77% for supraglottic or supracricoid hemilaryngopharyngectomy (with or without induction chemotherapy, neck dissection or postoperative radiotherapy) [205], [206], [207], [208], and between 70% and 73% for transoral laser microsurgery (with or without neck dissection or postoperative radiotherapy) [209], [210], [211]. The 5-year survival rates for stage III and IV hypopharyngeal carcinomas are 19%–37% for radiotherapy (with or without concomitant chemotherapy) [212], [213], [214], [215], and 47%–59% for transoral laser microsurgery (with or without neck dissection or postoperative radiotherapy) [209], [210]. Induction chemotherapy followed by radiotherapy achieved a 5-year survival rate of 38% in stage III and IV hypopharyngeal carcinomas [216].

Since survival cannot be improved in patients with hypopharyngeal cancer, the focus should be on improving the quality of life with organ-preserving therapy concepts in those patients with an unfavorable prognosis.

5.2 Partial Laryngopharyngectomy

The principle of *supracricoid hemilaryngopharyngectomy (SCHLP)* is to resect the tumor together with the piriform sinus, and the ipsilateral hemilarynx above the cricoid cartilage. After ipsilateral neck dissection is performed, the ipsilateral thyroid cartilage and half of the hyoid bone is resected. The infrahyoid muscles are dissected and rotated caudally and the larynx is opened by incision in the vallecula glossoepiglottica. Epiglottis and preepiglottic fat are then dissected in the vertical plane. The upper rim of the cricoid cartilage defines the caudal resection margin. After removal of the vocal fold and the ventricle, the posterior resection line is defined under direct vision. Following mobilization of the pharynx from the deep cervical fascia, the defect is closed by suturing the pharynx to infrahyoid muscles, laryngeal remnant and vallecula.

The *supraglottic hemilaryngopharyngectomy* is a modification of the supracricoid hemilaryngopharyngectomy with preservation of both vocal folds.

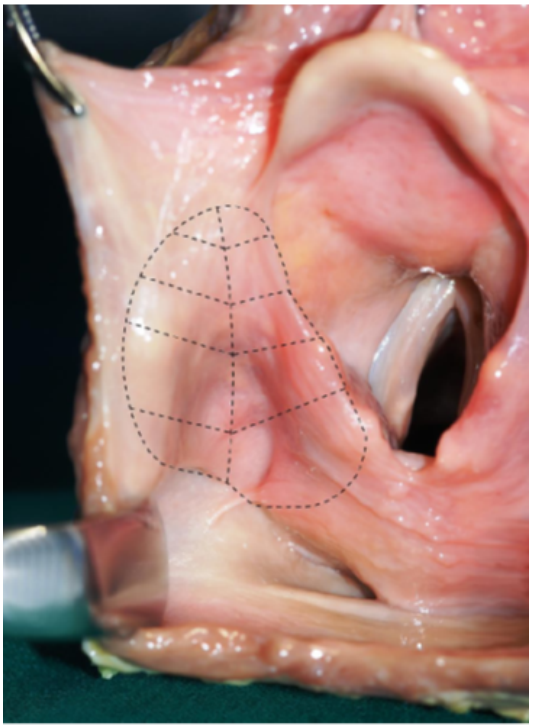

Figure 9: Anatomic specimen, non-fixed. The dotted lines show the resection in a case of a carcinoma of the piriform sinus.

Optimum exposure of the larynx and piriform sinus is essential for an adequate tumor resection with *transoral laser microsurgical partial laryngopharyngectomy*. The tumor is exposed with a bivalved laryngoscope and is resected step by step in the cranial-to-caudal direction (Figure 9). The position of the laryngoscope is adjusted several times as the resection proceeds in order to keep

both the tumor and the surrounding healthy tissue within the visual field of the microscope. Carcinomas of the piriform sinus are resected bloc wise to assess the extent of tumor infiltration to the depth. Aided by frozen section analysis of resection margins, preservation of a maximum amount of normal, healthy tissue is possible. Piriform sinus tumors are resected with a safety margin to the tumor of approximately 5–10 mm. If necessary, the resection can be extended to the oropharynx or the neighboring cervical soft tissue [3].

5.3 Oncologic Results

5.3.1 Results of Open Partial Laryngopharyngectomy

Ogura et al. [217] were the first to report on piriform sinus carcinomas treated with organ-preserving partial laryngopharyngectomy. They achieved a 3-year survival rate of 53% in highly selected patients with early piriform sinus carcinoma (mobile vocal cords, no tumor involvement of the apex of the piriform sinus, postcricoid region, or thyroid cartilage). However, 34% of patients required a secondary total laryngectomy due to local tumor recurrence [218]. Ogura's indications were subsequently adopted by several other laryngologists [219], [220], [221].
Henri Laccourreye et al. [222] reported in 1987 on 240 patients who underwent supracricoid hemilaryngopharyngectomy for early piriform sinus carcinomas. Local recurrences developed in 5.2% of cases. Eight per cent of patients required a tracheostoma and 15% suffered from dysphagia.
More recently, Chevalier et al. [205] published results of 31 patients with T1 and T2 piriform sinus carcinomas treated over a period of 15 years. Treatment consisted of supraglottic hemilaryngopharyngectomy with radical neck dissection and postoperative radiotherapy. While very good local control was achieved with this concept (local recurrences were observed in only 2% of patients), the survival rates were low, especially in patients with T2 tumors, due to a high incidence of recurrent metastases in the neck and distant metastases. All patients required temporary tracheostomy and temporary nasogastric tube feeding.
Makeieff et al. [206] reported on 87 patients with T1 and T2 piriform sinus carcinomas who underwent supraglottic hemilaryngopharyngectomy, neck dissection and postoperative radiotherapy in the years 1981–1998. In 19.5% of patients local tumor recurrences developed. Due to a large number of recurrent metastases in the neck and second primary carcinomas (amongst others 6.9% in the contralateral piriform sinus), the 5-year survival rate was as low as 60.3%. All patients required a temporary tracheostomy for a median time period of 16 days and 2 patients required permanent PEG tube feeding.
Foucher et al. [223] reported on 45 patients with T1-T2N0 hypopharynx carcinomas treated with partial pharyngolaryngectomy and elective neck dissection alone. The 5-year locoregional control rate with this treatment regimen was 82%.
Another organ-preserving treatment option in hypopharyngeal cancer is neoadjuvant chemotherapy followed by supracricoid hemilaryngopharyngectomy and postoperative radiotherapy. Ollivier Laccourreye and his group used this regimen to treat 118 patients with T1 and T2 carcinomas and 29 patients with T3 and T4a carcinomas of the piriform sinus between 1982 and 2000 [224]. Induction chemotherapy with cisplatin and 5-fluoruracil (2–6 cycles) received 97.4% of patients. Complete remission was clinically achieved in 21.7% and histopathologically proven in 16.8% of patients. Postoperative radiotherapy was given to 49.8% of patients. Only 8.2% of patient developed local tumor recurrence. The larynx preservation rate was 91.2% and the 5-year survival rate was 54.9%. The functional results were described in a consecutive publication [208]. The postoperative mortality rate was 3.7% and surgical complications, directly related to SCHLP occurred in 9.6% of cases. Patients received a nasogastric feeding tube for a median time period of 22 days. A permanent PEG feeding tube due to aspiration was needed in 0.7% of patients, 1.5% had to undergo completion laryngectomy and 0.7% died because of aspiration.

5.3.2 Results of Laser Microsurgery

The first results of 36 patients with hypopharyngeal cancer treated with laser microsurgery were published by Steiner and Herbst in 1987 [225]. Another report on 42 patients treated at the Department of Otorhinolaryngology at the University of Erlangen was published shortly after [226]. Between 1988 and 2001 a series of articles reported on results of transoral laser microsurgery in hypopharyngeal carcinomas [227], [228], [229].
Steiner et al. [209] performed primary laser microsurgery in curative intent in 129 previously untreated patients with squamous cell carcinoma of the piriform sinus in the years 1981–1996. The primary tumors were categorized according to the UICC/AJCC classification of 1992 as pT1 in 24 patients, pT2 in 74, pT3 in 17, and pT4 in 14 patients. Cervical lymph node metastases were present in 88 patients (68%) at the time of diagnosis. The tumors were distributed by stages as follows: stage I in 10 (8%) patients, stage II in 23 (18%), stage III in 26 (20%), and stage IV in 70 (54%). Unilateral or bilateral predominantly selective neck dissection was performed in 110 patients. Six (18%) patients with stage I and II and 69 (72%) with stage III and IV carcinomas were treated with adjuvant radiotherapy.
Local and locoregional recurrences developed in a total of 17 (13%) patients (stage I and II: 3/33, 9%; stage III and IV: 14/96, 15%). The Kaplan-Meier 5-year local control rate was 82% for stage I and II and 69% for stage III and IV. Eighteen (14%) patients developed late or recurrent metastases in the neck and 8 patients (6%) suffered metachronous distant metastases with locoregional tumor control. A metachronous second primary tumor was diagnosed in 24 (19%) patients. The Kaplan-Meier 5-year

overall survival rate was 71% for stage I and II and 47% for stage III and IV. The 5-year recurrence free survival rate was 95% for stage I and II and 69% for stage III and IV. Five (4%) patients had postoperative endolaryngeal bleeding, which was controlled endoscopically in all cases. Three patients required PEG tube feeding, one for a hypopharyngeal stenosis and two due to aspiration. All patients regained normal swallowing function.

In a follow up publication, Steiner and his group published in 2008 the results of 172 previously untreated patients with squamous cell carcinoma of the piriform sinus treated with primary laser microsurgery in curative intent in the years 1986–2003 [210]. Staging was done according to the UICC/AJCC 2002 classification. Twenty-one patients had pT1 tumors, 48 pT2, 75 pT3, and 28 pT4 tumors. The tumors were distributed by stages as follows: stage I in 7 (4%) patients, stage II in 19 (11%), stage III in 52 (30%), and stage IVa in 94 (55%) patients. Unilateral or bilateral predominantly selective neck dissection was performed in 93% of patients. Fifty-two per cent of patients were treated with adjuvant radiotherapy.

The Kaplan-Meier 5-year local control rate was 84% for pT1 lesions, 70% for pT2, 75% for pT3, and 57% for pT4a lesions. The 5-year recurrence free survival rate was 73% for stage I and II, 59% for stage III, and 47% for stage IVa. Permanent PEG tube feeding was required in 3.5% of patients and one patient had to undergo total laryngectomy due to functional impairment. In 3.5% of cases a tracheostomy was performed.

Rudert [230] reported the results of 29 patients with hypopharyngeal carcinomas who were treated with laser microsurgery at the University of Kiel between 1991 and 1995. Twenty-seven patients had T1 or T2 tumors. Eight (28%) patients developed local recurrences. The overall 5-year survival rate was 58% and the disease-specific survival rate was also 58%. In this study like in others, analysis showed that the survival rates depended strongly on cervical lymph node involvement. The 5-year survival rate was 74% for patients with N0 neck but only 34% for patients with cervical lymph node metastases. Accordingly, the survival rate was 78% for patients with stage I or II disease versus 35% for patients with stage III or IV disease. None of the patients required a tracheostomy together with the primary tumor surgery and all patients had normal postoperative swallowing function.

Vilaseca et al. [231] report on a cohort of 28 patients treated with transoral laser microsurgery, neck dissection and postoperative radiotherapy. Two patients had primary tumors classified as pT1, 16 as pT2, 9 as pT3, and 1 as pT4. The tumors were distributed by stages as follows: stage II in 21%, stage III in 29%, and stage IV in 50% of patients. The local control rate was 78%. The laryngeal function could not be maintained in 3 patients.

Karatzanis et al [211] analyzed retrospectively the course of disease in 119 patients with T1 and T2 hypopharyngeal carcinomas who were treated with transoral laser microsurgery, neck dissection, and with or without adjuvant radiotherapy at the University of Erlangen between 1979 and 2004. The 5-year local control rate was 90% for 45 pT1 and 84% for 74 pT2 carcinomas. The 5-year disease-specific survival was 78% for pT1N0/N+ and 70% for pT2N0/N+ cases. Permanent tracheostomy or PEG feeding was required in a total of 5% of patients.

5.3.3 Results of Radiotherapy

Primary radiotherapy of the primary tumor and both sides of the neck achieved good local control rates and disease-specific survival rates, particularly in T1 and T2 carcinomas of the upper piriform sinus. However, the local control rate declines when the tumor volume exceedes 6.5 ml. In addition, an increased risk for a functionless larynx was seen with increasing tumor volume, even when local tumor control was achieved [232]. Furthermore, it is known, that operations for tumor recurrences after primary radiotherapy are associated with complications in a high percentage of cases. About 30%–35% of patients after secondary laryngectomy developed pharyngocutaneous fistulas [233].

Pameijer et al. [234] reported a local control rate of 78% for 23 T1 and T2 carcinomas treated with primary radiotherapy between 1984 and 1993. The local control rate declined when the apex of the piriform sinus was involved by carcinoma and the tumor volume exceeded 6.5 ml. In a subsequent publication from the same institution, the 5-year local control rate was 90% for T1 tumors and 80% for T2 tumors. Local control with organ preservation was 86% for patients with T1 tumors and 82% for patients with T2 carcinomas [235]. Garden et al. [201] achieved a local control rate of 75.5% in 57 T1 and T2 hypopharyngeal carcinomas. Wang [202] reported a 5-year local control rate of 74% for T1 carcinomas and 76% for T2 carcinomas. The 5-year rates for disease-free survival were 73% for T1 tumors and 68% for T2 tumors. In contrast, Jones [236] reported a 5-year disease-specific survival rate of only 40% for T1 carcinomas and 28% for T2 carcinomas. In 2006, Nakamura et al. [203] described 115 patients with T1 and T2 piriform sinus carcinomas treated with primary radiotherapy at different Japanese hospitals. The local control rate was 77% for T1 and 63% for T2 carcinomas with an overall 5-year disease-specific survival rate of 77%. Rabbani et al. [237] and Yoshimura et al. [204] treated 26 and 77 patients with early hypopharyngeal carcinomas and achieved a local control rate of 86% and 70%, and a 5-year disease-specific survival rate of 85% and 74%, respectively.

Radiotherapy is generally combined with chemotherapy in patients with locally advanced carcinomas of the hypopharynx (stage III, IVa). However, chemoradiotherapy has only slightly improved survival rates. Recent data has shown that concomitant chemoradiotherapy has advantages over other chemoradiation protocols with respect to locoregional control [238], [239], [240], but at the cost of higher toxicity [218], [232], [241].

About 50% of patients with locally advanced hypopharyngeal carcinomas develop local recurrences after primary (chemo)-radiotherapy and the 5-year survival rate averages between 5%–30% [199], [202], [236], [242], [243],

[244], [245]. It should be added that many studies have demonstrated, that in about 30% of patients severe functional disabilities result. Particularly swallowing difficulties caused by impaired motility, strictures of the hypopharynx or upper esophagus, are observed as side effects of chemoradiation [246], [247], [248], [249].
The results of salvage treatment after (chemo-)radiotherapy are poor [201], [250], [251], [252], [253] and many of those patients do not qualify for surgery. In a report by Taki et al. [254] only 12 out of 41 patients with a recurrence could undergo surgery. In only 7 cases surgery was successful. The risk of pharyngocutaneous fistulas in secondary laryngectomy is increased if surgery must be performed within the first couple of months after radiotherapy. Radiation doses of over 64 Gray and concomitant chemoradiotherapy increase the risk of pharyngocutaneous fistulas [233], [254].
Another nonsurgical organ-preservation approach in head and neck cancer is neoadjuvant chemotherapy with cisplatin and 5-fluorouracil combined with radiotherapy. A review of clinical trials conducted between 1970 and 1995 and a meta-analysis of previously published data show no clear evidence for an improvement in locoregional tumor control or survival rates or a decrease in the incidence of metachronous distant metastases [255], [256]. Nevertheless, induction chemotherapy has become a widely accepted treatment modality for advanced head and neck cancers, particularly in the USA [255], [257].
A randomized phase III study for hypopharynx carcinomas was conducted by the European Organization for Research and Treatment of Cancer (EORTC 24891) [258]. In two arms, induction chemotherapy followed by radiotherapy was compared with primary laryngopharyngectomy followed by postoperative radiotherapy. In the "chemotherapy" arm (n=100 patients), 54% of patients had complete remission at the primary site and 51% at the regional lymphatics, Patients who did not respond to chemotherapy underwent surgery (total laryngectomy with partial pharyngectomy) and postoperative irradiation. Patients who developed a tumor recurrence following chemotherapy and irradiation also underwent surgery. No differences were found between the two treatment arms with respect to local and regional tumor control. The 5-year disease-specific survival rate was 29% in the "chemotherapy" arm and 36% in the "surgery" arm. The likelihood of being alive with a functional larynx 5 years after treatment was 35%. This figure was corrected to 22% after final analysis of the study [216].
The authors conclude from their results that induction chemotherapy followed by radiotherapy can be used for organ preservation in cancer of the hypopharynx without compromising survival. A critical analysis of the study, however, shows that for various reasons only 52 out of 100 patients completed their chemotherapy cycles according to the study protocol. This resulted in a relatively small number for the definitive evaluation. The complication rate, including two treatment-related deaths, was remarkably high. While 94% of the patients had stage III or IV disease, 38 patients had T2 primary tumors with intact vocal cord mobility. These patients most probably, could have been treated with organ-preserving surgery. "Needing radical surgery" appears to have been a rather subjective inclusion criterion.
In a subsequent phase III study (EORTC 24954) induction chemotherapy followed by radiotherapy (n=224) was compared with simultaneous chemoradiotherapy (n=226) in patients with resectable larynx carcinomas (T3/T4N0-N2) or with hypopharynx carcinomas (T2-T4N0-N2) [259]. No significant differences could be shown between these two therapy arms with respect to organ preservation, overall survival, and toxicity.
A study of the University of Michigan examined the efficacy of neoadjuvant chemotherapy with carboplatin and 5-fluorouracil followed by radiotherapy in 55 patients with oropharyngeal cancer and 34 patients with hypopharyngeal cancer (stages II-IV) [260]. In 59% of patients with hypopharyngeal cancer larynx preservation was achieved at the end of treatment. At the time the study was evaluated finally, 29% of the patients with hypopharyngeal cancer were still alive with a functional larynx and the 5-year survival rate was 24%. It should also be noted that 26% of patients included in the trial had T1 or T2 primary tumors and presumably would have been candidates for organ-preserving surgery.
Another approach involves modifications of induction chemotherapy and of fractionating radiotherapy. In a phase II study induction chemotherapy with paclitaxel/cisplatin followed by accelerated and hyperfractionated (concomitant boost) radiotherapy was performed in patients with larynx or hypopharynx cancer who had responded to chemotherapy [261]. The 3-year survival rate with preserved and functional larynx was 43% with tolerable late toxicity.

5.4 Conclusion

In summary, the data show that primary radiotherapy of "low-volume" T1 and T2 carcinomas of the hypopharynx is associated with good local control rates. Definitive radiotherapy in "high-volume" T2, T3, and T4 carcinomas increases both the likelihood for local recurrence and the risk of severe swallowing disorders.
Favorable local control rates were also reported for supracricoid or supraglottic hemilaryngopharyngectomy in selected T1, T2, and T3 carcinomas. However, high morbidity caused by the surgical procedure itself and preliminary induction chemotherapy, which is obligatory in some centers, have to be taken into account. With transoral laser microsurgery combined with selective neck dissection and adjuvant radiotherapy complication rates are considerably lower compared to open partial laryngopharyngectomy. No lethal complications were reported following laser microsurgery. Postoperative morbidity was significantly lower, and the 5-year recurrence-free and overall survival rates significantly higher. Furthermore, transoral laser microsurgery has a much wider spectrum of indications than supracricoid or supraglottic hemilaryngopharyngectomy.

With transoral laser microsurgery very favorable local control rates were achieved in T1 and T2 carcinomas. The tumor volume has no influence on local control in contrast to primary radiotherapy. Morbidity and complication rates are lower than with open surgery or with radiotherapy. Both open partial laryngopharyngectomy and transoral laser microsurgery are superior to primary radiotherapy with respect to larynx preservation. In case of pathohistologically uninvolved lymph nodes, adjuvant radiotherapy is not needed. Generally, transoral laser microsurgery is suitable for T3 carcinomas with intact vocal cord mobility and for selected cases with vocal cord fixation. Tumor infiltration into adjacent organs, such as the oropharynx, is not regarded to be a contraindication for transoral laser microsurgery.

According to the current literature, preservation of a functional larynx can be achieved in one third of cases treated with induction chemotherapy followed by radiotherapy. Results for modified chemotherapy and radiotherapy protocols have yet to be expected.

Patients in whom transoral laser microsurgery is no longer possible, and who foreseeable have a high risk for recurrence or functional impairment with primary chemoradiation, should better be treated surgically with total laryngectomy, partial pharyngectomy and postoperative radiotherapy.

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Corresponding author:

Prof. Dr. med. Petra Ambrosch, MD
Department of Otorhinolaryngology – Head and Neck Surgery, Christian-Albrechts-University of Kiel, Arnold-Heller-Str. 14, 24105 Kiel, Germany
ambrosch@hno.uni-kiel.de

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